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E-mail: jzus@zju.edu.cn

Correspondence:

Difference in survival between right- versus left-sided colorectal neuroendocrine neoplasms*#

Ge-han XU[1], Hua-wei ZOU[†‡2], Ashley B. GROSSMAN[3]

[1]*The Second Clinical College of China Medical University, Shenyang 110004, China*

[2]*1st Department of Oncology, Shengjing Hospital Affiliated to China Medical University, Shenyang 110022, China*

[3]*NET Unit, ENETS Centre of Excellence, Royal Free Hospital, London NW3 2QG, UK*

[†]E-mail: zhw20181102@sina.com

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Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors that arise from neuroendocrine cells, and in some cases are capable of producing agents that may cause characteristic hormonal syndromes (Cives and Strosberg, 2018). Such tumors were previously thought to be rare, but the rate of detection of NENs, especially from the gastrointestinal tract, is increasing with the widespread use of colonoscopy, cross-sectional imaging, and biomarkers (Gu et al., 2019). A study based on the Surveillance, Epidemiology, and End Results (SEER) database showed that the age-adjusted incidence of NENs increased 6.4-fold from 1973 (1.09 per 100000) to 2012 (6.98 per 100000) (Dasari et al., 2017), while there was a progressive increase in the incidence of colorectal NENs (Starzyńska et al., 2017).

Colorectal NENs are mostly non-functional, and while often presenting similarly to adenocarcinomas, are both pathologically and in terms of their behavior quite distinct (Portale et al., 2012; Cesar et al., 2013). It has long been widely recognized that there are distinct differences in terms of the epidemiology, clinical manifestations and prognosis between right- and left-sided colorectal adenocarcinomas, with the National Comprehensive Cancer Network (NCCN) guidelines (Benson et al., 2017) confirming the significance of the primary tumor location in the treatment of metastatic colorectal cancer (mCRC). However, the difference between right- and left-sided colorectal NENs has been little investigated. In order to clarify this issue, we have used the SEER database to compare survival between right- and left-sided colorectal NENs, neuroendocrine tumors (NETs), and neuroendocrine carcinomas (NECs), and reported significant and clinically relevant differences in this study.

We selected all patients with colorectal NENs from the SEER database (1988 to 2014). Patients were identified based on the International Classification of Diseases for Oncology, 3nd Edition (ICD-O-3) codes 8013, 8041, 8042, 8044, 8045, 8240, 8243–8246, and 8249. Tumor location was identified by ICD-O-3 codes C18.0–C18.7, C19.9, and C20; tumors of the appendix (C18.1), overlapping lesions of colon (C18.8), colon, and NOS (not otherwise specified; C18.9) were excluded. Patients aged 18 years and older with pathologically confirmed colorectal NENs and without a history of other cancers were included. Patients who were lost to follow-up and had cancers with unknown differentiation and incomplete staging information were excluded.

Tumors occurring from the cecum to the transverse colon were defined as right-sided cancers, and those occurring from the splenic flexure to the rectum as left-sided cancers. Tumor, node, and metastasis (TNM) status was assigned according to American

‡ Corresponding author

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ORCID: Ge-han XU, https://orcid.org/0000-0002-0979-6792

Joint Committee on Cancer (AJCC) stage group (8th Edition). Survival time was calculated as the period from the date of diagnosis until death or the last time of follow-up (December 31, 2014). We used cancer-specific survival as the main study outcome to evaluate differences in survival. Individuals who were alive at last follow-up or who died from non-NEN causes were treated as censored observations. Appropriate statistical analysis was performed with the SPSS 21.0 statistics software (including Chi-square test, Kaplan-Meier method, and Cox proportional hazard regression). We also included a stage–location interaction term in the model because of the significant interaction between stage and tumor location (P<0.001). All tests of significance used two-sided P values at the P<0.05 level.

A total of 4136 patients were included in this study (Table 1). The median age at diagnosis was 58.0 years (mean, 59.4 years). Left-sided colorectal NENs were noted in 63.0% of patients (n=2607), of which the most frequent site was the rectum (87.4%), while 37.0% (n=1529) had right-sided colonic NENs, of which the most frequent site was the cecum (60.7%). Patients with right-sided colonic NENs, compared with those who had left-sided colorectal NENs, were slightly more likely to be female (53.0% vs. 49.0%, P=0.013), and were significantly older (61.6% vs. 37.6%; P<0.001). The majority of the right-sided colonic NENs were stage IV (48.3%) and poorly differentiated (39.8%), while those on the left were mainly stage I (63.8%) and highly differentiated (61.9%).

Univariate survival analysis demonstrated that right-sided colonic NENs had a significantly worse survival than left-sided colorectal NENs (5-year survival rate 72.2% vs. 41.8%; P<0.001), while multivariate analysis confirmed that right-sided colonic NENs had a higher risk of death than left-sided colorectal NENs (hazard ratio (HR), 2.13; 95% confidence interval (CI), 1.31–3.46; P=0.002) (Table S1). However, this relationship was not consistent across tumor stage (Fig. 1). Multivariate analysis confirmed that right-sided colonic NENs had a higher risk of death than left-sided colorectal NENs in stage I (HR, 19.31; 95% CI, 3.80–98.10; P<0.001) and stage IV (HR, 1.16; 95% CI, 1.01–1.33; P=0.033), while stage III right-sided colonic NENs had a lower risk of death (HR, 0.68; 95% CI, 0.54–0.86; P=0.001), with no significant difference in risk of death between right- and left-sided colorectal NENs for stage II (HR, 0.72; 95% CI, 0.41–1.28; P=0.267).

Table 1 Demographics and clinical characteristics of patients with colorectal NENs

Characteristics	Overall (n=4136)	Left-sided (n=2607; 63.0%)	Right-sided (n=1529; 37.0%)	P
Sex				0.013
Women	2089 (50.5%)	1278 (49.0%)	811 (53.0%)	
Men	2047 (49.5%)	1329 (51.0%)	718 (47.0%)	
Race				<0.001
White	2899 (70.1%)	1623 (62.3%)	1276 (83.5%)	
Black	692 (16.7%)	511 (19.6%)	181 (11.8%)	
Asian or Pacific islander	473 (11.4%)	405 (15.5%)	68 (4.4%)	
Unknown	72 (1.7%)	68 (2.6%)	4 (0.3%)	
Age (years)				<0.001
<60	2215 (53.6%)	1628 (62.4%)	587 (38.4%)	
≥60	1921 (46.4%)	979 (37.6%)	942 (61.6%)	
Tumor stage				<0.001
I	1700 (41.1%)	1664 (63.8%)	36 (2.4%)	
II	337 (8.1%)	195 (7.5%)	142 (9.3%)	
III	868 (21.0%)	256 (9.8%)	612 (40.0%)	
IV	1231 (29.8%)	492 (18.9%)	739 (48.3%)	
Tumor grade				<0.001
Well differentiated	2026 (49.0%)	1614 (61.9%)	412 (26.9%)	
Moderately differentiated	603 (14.6%)	362 (13.9%)	241 (15.8%)	
Poorly differentiated	1014 (24.5%)	406 (15.6%)	608 (39.8%)	
Undifferentiated	493 (11.9%)	225 (8.6%)	268 (17.5%)	
Surgery				0.657
No/unknown	778 (18.8%)	485 (18.6%)	293 (19.2%)	
Yes	3358 (81.2%)	2122 (81.4%)	1236 (80.8%)	

Data are expressed as number (percentage)

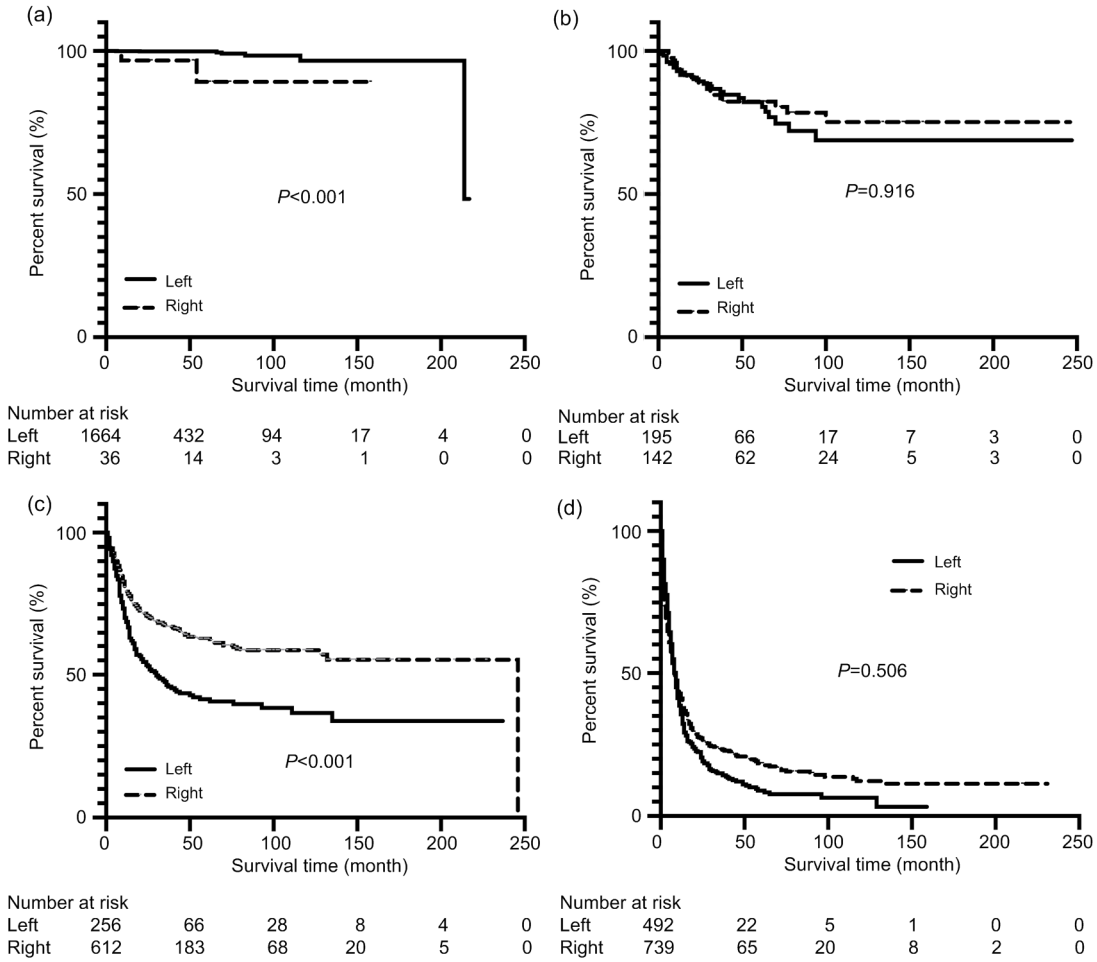

Fig. 1 Kaplan-Meier survival estimates for patients with right- and left-sided colorectal NENs
(a) Stage I disease; (b) Stage II disease; (c) Stage III disease; (d) Stage IV disease

We subsequently analyzed differences in survival just between the rectal and cecal NENs (Fig. 2). There was no difference in risk of death between these two tumors for stages I, II, and IV (P=0.990, P=0.369, and P=0.213, respectively), while cecal NENs had a lower risk of death in stage III (P=0.013). Then, specifically excluding the rectal and cecal NENs, no significant difference in risk of death between right- and left-sided colorectal NENs was seen for stage I (not available (NA); P=0.471), stage II (HR, 1.21; 95% CI, 0.34–4.35; P=0.773), stage III (HR, 0.76; 95% CI, 0.53–1.09; P=0.132), or stage IV (HR, 1.09; 95% CI, 0.87–1.36; P=0.471) tumors (Table 2).

Then cancers with highly and moderately differentiated NENs were defined as NETs, while those with poorly-differentiated and undifferentiated NENs were defined as NECs. Because the biological behaviors of NETs and NECs were significantly different (5-year survival rate 86.4% vs. 17.5%; P<0.001), we subsequently compared the prognostic difference between right- and left-sided colorectal NETs and NECs, respectively. For colorectal NETs, there was no significant difference in risk of death between right- and left-sided colorectal NETs for stage I (NA; P=0.923), stage II (HR, 4.62; 95% CI, 0.37–57.09; P=0.233), stage III (HR, 0.78; 95% CI, 0.38–1.60; P=0.496), or stage IV (HR, 0.76; 95% CI, 0.39–1.48; P=0.411) after excluding the rectal and cecal NETs. For colorectal NECs, there is also no significant difference in risk of death between right- and left-sided colorectal NECs for stage I (NA), stage II (HR, 0.72; 95% CI, 0.19–2.71; P=0.623), stage III (HR, 0.70; 95% CI, 0.46–1.08; P=0.106), or stage IV (HR, 1.13; 95% CI, 0.89–1.44; P=0.302) after excluding the rectal and cecal NECs.

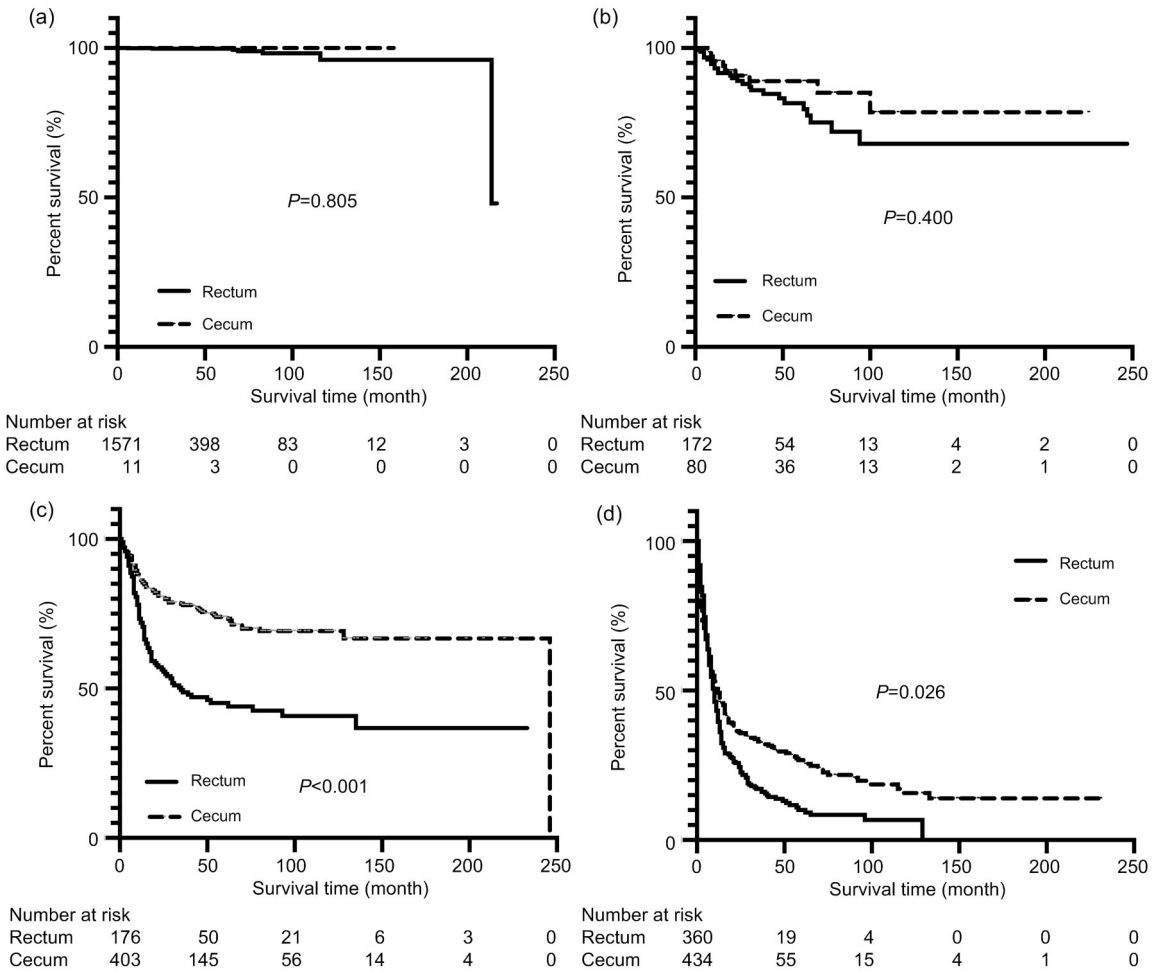

Fig. 2 Kaplan-Meier survival estimates for patients with rectal and cecal NENs
(a) Stage I disease; (b) Stage II disease; (c) Stage III disease; (d) Stage IV disease

Table 2 Multivariable Cox regression for cancer-specific risk of death by stage[a]

NEN location	Stage I			Stage II			Stage III			Stage IV		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Left side	1.00			1.00			1.00			1.00		
Right side	19.31	3.80–98.10	<0.001	0.72	0.41–1.28	0.267	0.68	0.54–0.86	0.001	1.16	1.01–1.33	0.033
Rectum	1.00			1.00			1.00			1.00		
Cecum	NA	NA	0.990	0.70	0.32–1.52	0.369	0.67	0.48–0.92	0.013	1.12	0.94–1.34	0.213
Left side[b]	1.00			1.00			1.00			1.00		
Right side[b]	NA	NA	0.365	1.21	0.34–4.35	0.773	0.76	0.53–1.09	0.132	1.09	0.87–1.36	0.471

[a] Cox regression controlling for sex, ethnicity, age, and surgery; [b] Exclude rectal NEN and cecal NEN. HR, hazard ratio; CI, confidence interval; NA, not available

This study compared the differences in survival between right- and left-sided colorectal NENs based on the SEER database. Differences in clinical presentation and tumor biology between right- and left-sided colorectal adenocarcinomas have been reported in several publications. Compared with left-sided colorectal adenocarcinomas, right-sided colon adenocarcinomas at diagnosis are more advanced in tumor size, vessel invasion, and lymphocytic infiltration (Meguid et al., 2008; Snaebjornsson et al., 2010;

Price et al., 2015; Mik et al., 2017). Although their biological behavior is different from adenocarcinoma, in this study we still found that the right-sided colonic NENs were seen in significantly older patients, present at a higher stage, and are more likely to be poorly differentiated compared to left-sided lesions. All these factors lead to a worse prognosis for patients with right-sided colonic NENs.

However, this phenomenon is not consistent across tumor stage, the survival advantage in left-sided colorectal NENs becoming less prominent with increase in staging, such that stage III left-sided colorectal NENs are associated with a relatively higher risk of death. In a study of 35618 patients with NENs based on the SEER database, Yao et al. (2008) reported the difference in survival between rectal and cecal NENs. Rectal NENs showed a better survival than cecal NENs when localized, but showed a worse survival when they demonstrated regional invasion or metastases. As rectal and cecal NENs are the predominant colorectal NENs, we further explored whether these tumors are responsible for the difference in survival between right- and left-sided colorectal NENs across tumor stage. It was found that the survival difference between right- and left-sided colorectal NENs disappeared for each stage when excluding the rectal and cecal NENs, and this was also consistent in colorectal NETs/NECs. Therefore, we found that it is the difference between rectal and cecal NETs/NECs, which affects the difference in survival between right- and left-sided colorectal NETs/NECs across tumor stage in our study.

We believe that several factors may contribute to this inconsistent difference in survival between right- and left-sided colorectal NENs across tumor stage, including subsequent treatment. Surgery is the preferred treatment for colorectal NENs, analogous to those in colorectal adenocarcinomas (Clark et al., 2009; Starzyńska et al., 2013). Stage I rectal NENs may show a better outcome with endoscopic submucosal dissection (ESD) or transanal endoscopic microsurgery (TEM). However, no difference in survival was found between rectal and cecal NENs in stage I, which we thought could be attributed to the small number of cecal NENs. The reason for the better survival of right-sided colorectal NENs in stage III remains unclear. First, we speculate that different surgical procedures may partially account for it. Total mesorectal excision (TME) or abdominoperineal amputation is recommended for rectal NENs, while resection with lymphadenectomy is recommended for cecal NENs in stage III. Second, it is possible that some cecal lesions actually arise from the appendix and extend into the cecum (Modlin et al., 2003); this process may cause the cecal NENs to show apparently better survival than rectal NENs in relation to the improved survival of appendiceal NENs. Third, microsatellite instability (MSI) may also account for this aspect: many studies have demonstrated that patients with MSI tumors have a better survival and MSI status is an independent favorable predictor of survival. MSI is predominantly seen more in right-sided colorectal adenocarcinomas than in left-side (Jernvall et al., 1999; Popat et al., 2005). Sahnane et al. (2015) found that the MSI frequency in gastrointestinal NECs is similar to that of adenocarcinoma. Finally, adjuvant chemotherapy for stage III colorectal NETs is not uniformly recommended. However, it is an important treatment for stage III NEC patients (Garcia-Carbonero et al., 2016; Dasari et al., 2017). Platinum derivatives combined with etoposide and cisplatin/carboplatin (EP/EC) are the preferred option (Mitry et al., 1999). There is little information on the differential efficacy of EP/EC between right- and left-sided colorectal NENs. To date, only a single publication (Patta and Fakih, 2011) reviewed eight cases with metastatic colorectal NECs, reporting that patients with rectal NECs showed significantly better survival than those with colonic NECs, thus suggesting that different primary tumors may respond differently to EP/EC.

This study has several limitations. First, some of the surgical information was uncertain about the exact procedure, and the SEER database does not record information of other treatment strategies such as adjuvant chemotherapy, which may impact on survival. Second, the grading of the NENs may be incorrectly made in non-expert centers, and Ki-67 is not recorded. Finally, this is a retrospective study, and while the overall numbers are large, the numbers of patients in some of the subgroup analyses are relatively few.

Despite these limitations, our study shows the difference in survival between right- and left-sided colorectal NENs, and more importantly, we have demonstrated the influence of rectal and cecal NENs on the survival difference between right- and left-sided colorectal NENs.

Contributors

Ge-han XU collected and analyzed the data, and wrote the manuscript. Hua-wei ZOU and Ashley B. GROSSMAN contributed to the study design, data analysis, writing and editing of the manuscript. All authors have read and approved the final manuscript and, therefore, had full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Ge-han XU, Hua-wei ZOU, and Ashley B. GROSSMAN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Benson AB III, Venook AP, Cederquist L, et al., 2017. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*, 15(3):370-398. https://doi.org/10.6004/jnccn.2017.0036

Cesar D, Zanatto RM, da Silva MV, et al., 2013. Colon and rectum neuroendocrine tumors: experience of the National Cancer Institute in Brazil. *Arq Bras Cir Dig*, 26(1): 36-39. https://doi.org/10.1590/S0102-67202013000100008

Cives M, Strosberg JR, 2018. Gastroenteropancreatic neuroendocrine tumors. *CA Cancer J Clin*, 68(6):471-487. https://doi.org/10.3322/caac.21493

Clark OH, Benson AB III, Berlin JD, et al., 2009. NCCN clinical practice guidelines in oncology: neuroendocrine tumors. *J Natl Compr Canc Netw*, 7(7):712-747. https://doi.org/10.6004/jnccn.2009.0050

Dasari A, Shen C, Halperin D, et al., 2017. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*, 3(10):1335-1342. https://doi.org/10.1001/jamaoncol.2017.0589

Garcia-Carbonero R, Sorbye H, Baudin E, et al., 2016. ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology*, 103(2):186-194. https://doi.org/10.1159/000443172

Gu Q, Lin YM, Cen L, et al., 2019. Endoscopic ultrasonography is useful in the diagnosis and treatment of rectal neuroendocrine neoplasms: a case series. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 20(10):861-864. https://doi.org/10.1631/jzus.B1900168

Jernvall P, Mäkinen MJ, Karttunen TJ, et al., 1999. Microsatellite instability: impact on cancer progression in proximal and distal colorectal cancers. *Eur J Cancer*, 35(2): 197-201. https://doi.org/10.1016/S0959-8049(98)00306-2

Meguid RA, Slidell MB, Wolfgang CL, et al., 2008. Is there a difference in survival between right- versus left-sided colon cancers? *Ann Surg Oncol*, 15(9):2388-2394. https://doi.org/10.1245/s10434-008-0015-y

Mik M, Berut M, Dziki L, et al., 2017. Right- and left-sided colon cancer—clinical and pathological differences of the disease entity in one organ. *Arch Med Sci*, 13(1):157-162. https://doi.org/10.5114/aoms.2016.58596

Mitry E, Baudin E, Ducreux M, et al., 1999. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer*, 81(8):1351-1355. https://doi.org/10.1038/sj.bjc.6690325

Modlin IM, Lye KD, Kidd M, 2003. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*, 97(4):934-959. https://doi.org/10.1002/cncr.11105

Patta A, Fakih M, 2011. First-line cisplatin plus etoposide in high-grade metastatic neuroendocrine tumors of colon and rectum (MCRC NET): review of 8 cases. *Anticancer Res*, 31(3):975-978.

Popat S, Hubner R, Houlston RS, 2005. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol*, 23(3):609-618. https://doi.org/10.1200/JCO.2005.01.086

Portale TR, Branca A, Pesce A, et al., 2012. Neuroendocrine carcinoma of colon and rectum: a rare neoplasia with a poor prognosis. *Minerva Chir*, 67(3):283-284.

Price TJ, Beeke C, Ullah S, et al., 2015. Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? *Cancer*, 121(6):830-835. https://doi.org/10.1002/cncr.29129

Sahnane N, Furlan D, Monti M, et al., 2015. Microsatellite unstable gastrointestinal neuroendocrine carcinomas: a new clinicopathologic entity. *Endocr Relat Cancer*, 22(1): 35-45. https://doi.org/10.1530/ERC-14-0410

Snaebjornsson P, Jonasson L, Jonsson T, et al., 2010. Colon cancer in Iceland—a nationwide comparative study on various pathology parameters with respect to right and left tumor location and patients age. *Int J Cancer*, 127(11): 2645-2653. https://doi.org/10.1002/ijc.25258

Starzyńska T, Deptała A, Królicki L, et al., 2013. Colorectal neuroendocrine neoplasms—management guidelines (recommended by the Polish Network of Neuroendocrine Tumours). *Endokrynol Pol*, 64(6):494-504. https://doi.org/10.5603/EP.2013.0032

Starzyńska T, Londzin-Olesik M, Bałdys-Waligórska A, et al., 2017. Colorectal neuroendocrine neoplasms—management guidelines (recommended by the Polish Network of Neuroendocrine Tumours). *Endokrynol Pol*, 68(2):250-260. https://doi.org/10.5603/EP.2017.0019

Yao JC, Hassan MM, Phan A, et al., 2008. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*, 26(18):3063-3072 https://doi.org/10.1200/JCO.2007.15.4377

List of electronic supplementary materials

Table S1 Multivariable Cox regression of independent variables for cancer-specific risk of death

中文概要

题　目：左右半结直肠神经内分泌肿瘤的生存差异研究

目　的：研究不同分期下左右半结直肠神经内分泌肿瘤（NEN）的生存差异。

创新点：左右半结直肠腺癌的生存差异已得到深入研究，而结直肠 NEN 作为一罕见病理类型，其左右半的生存差异尚缺乏研究。本研究旨在明确这一问题。

方　法：选取 SEER 数据库中 1988~2014 年经病理确诊的结直肠 NEN 患者进行回顾性研究。多因素 Cox 回归分析比较左右半结直肠 NEN 的生存差异。

结　论：相比于左半结直肠 NEN，右半结肠 NEN 具有显著升高的死亡风险。而直肠与盲肠 NEN 是不同分期下左右半结直肠 NEN 生存差异的主要影响因素。

关键词：神经内分泌肿瘤；结直肠；生存