



Factors associated with worse outcomes for colorectal neuroendocrine tumors in radical versus local resections

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Background: Colorectal neuroendocrine tumors (NETs) are the most common NETs of the gastrointestinal tract. Due to the rarity, colorectal NETs are understudied and are not clearly understood. Our study sought to identify the factors associated with worse outcomes for colorectal NETs following resection.

Methods: We identified patients diagnosed with colorectal NETs [2004–2014] who underwent resection from the National Cancer Data Base. Non-NETs were excluded. Overall survival (OS) was evaluated using the Kaplan Meier method. Cox proportional hazards and logistic regression models were used to assess factors associated with radical versus local resection, OS and LOS.

Results: A total of 7,967 colon and 11,929 rectal NETs were analyzed. The majority of colon (93.4%) and rectal (89.1%) NETs underwent radical and local resection respectively. The 5-year OS was 69% and 92% for colon and rectal NETs respectively. Older age (OR 1.45, CI 1.37–1.53) and clinical stage 4 (OR 9.91, CI 4.56–21.52) were associated with higher odds for colonic radical resection. Lowest median income quartile (OR 1.41, CI 1.21–1.64) and African Americans (OR 1.26, CI 1.07–1.49) experienced higher mortality for colon and rectal NETs respectively.

Conclusions: Racial minority and low-income patients experience worse outcomes for colorectal NETs following resection.

Keywords: Neuroendocrine neoplasms; neuroendocrine tumors (NETs); neuroendocrine carcinoma (NEC); colorectal cancer; radical resection; endoscopic resection; outcomes; National Cancer Data Base

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies that arise from the cells of the neuroendocrine system. Although these cells are distributed throughout the body, the most common site of disease is the gastrointestinal (GI) tract (1). Rectal NETs account for up to 27% of all NETs and 20% of gastrointestinal NETs

(2–4). Colon NETs, which are less frequent, account for only 9.6% of all NETs and 14.1% of gastrointestinal NETs (2–8). Due to the rarity of these tumors, colorectal NETs are understudied and are not clearly understood. Additionally, advances in screening endoscopy and increased detection rates have resulted in an increase in the incidence of colorectal NETs in recent years (9–12), thus increasing the burden of this disease in the general population as well

as demanding greater attention than in the past.

Although rectal NETs are more common, they exhibit a more favorable prognosis. Prior large US population-based studies reported a 5-year cancer-specific survival of 87.5–89.9% for localized rectal NETs (3–5). In contrast, colon NETs displayed the worst prognosis, with 5-year survival rates of between 23% and 42% in the 1990s (5,8,13). The poor prognosis of colon NETs has been attributed to the larger tumor size, earlier nodal involvement or metastasis, and poorer histologic differentiation of this subset of gastrointestinal NETs (8,14). Regardless of the location, clinicopathologic characteristics of gastrointestinal NETs, such as tumor size, tumor depth and lymph node metastases, are well documented determinants of treatment modality and outcomes (15,16). Prior studies suggest that small sized colorectal NETs (<10 mm) and without lymph node involvement can be safely treated with local resection, while larger tumors with size >10 mm or those with lymphatic invasion would require radical resection (2,6,10,17,18). Additionally, the presence of metastases is associated with worse patient outcomes and poor survival (2,17). However, there is a paucity of data regarding the clinical outcomes of patients who underwent radical and local resections for colorectal NETs. It is also not currently clear if chemotherapy has an impact on outcomes for patients who undergo resection. Additionally, the impact of baseline patient social and demographic characteristics on treatment modality and patient outcomes are not clearly understood.

To address these issues, our study sought to identify the patient-related factors associated with radical versus local resection for colon and rectal NETs in a national cohort of patients. We also sought to determine how these factors influence patient outcomes for colon and rectal NETs following resection. We hypothesized that treatment modality (i.e., radical versus local resection), and patient outcomes such as mortality and hospital length of stay are influenced by pertinent patient social and demographic characteristics. We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (19) (available at: <http://dx.doi.org/10.21037/jgo-20-193>).

Methods

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society.

The CoC's NCDB and the hospital participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors. The NCDB is a national cancer registry which captures 70% of all new cancer diagnoses in the United States from 1,500 cancer facilities and collects patient demographics and tumor and treatment characteristics. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was exempt from IRB review and patients' informed-consent due to its use of de-identified data.

We identified patients diagnosed with invasive colon and rectal cancer between 2004 and 2014 who underwent a surgical resection from the National Cancer Data Base. We excluded patients diagnosed with a non-NET histology as well as those who did not undergo a local or radical resection (*Figure 1A,B*). Variables included in analysis were patient demographics (age, sex, race, Spanish/Hispanic origin, Charlson-Deyo score, primary payer, income, and education), treatment characteristics (resection type and chemotherapy), and tumor characteristics (clinical stage, surgical margins, and both number of lymph nodes examined and number of positive lymph nodes).

Statistical analysis

Patient demographics and treatment and tumor characteristics were described within each tumor site. Categorical variables were described as number and percentage and continuous variables as median and interquartile range (IQR). Overall survival (OS) was evaluated from time of resection to death or last follow-up using the Kaplan Meier method. Cox proportional hazards regression models were used to assess factors associated with OS and length of stay. Logistic regression models were used to evaluate factors associated with radical versus local resection and those having 12+ lymph nodes removed. All multivariable models were stratified by tumor site. Odds ratio (OR) and 95% confidence intervals (CI) are reported. Analyses were performed using SAS version 9.4 and P values <0.05 were considered statistically significant.

Results

Colon NETs

A total of 7,967 NETs of the colon were identified and

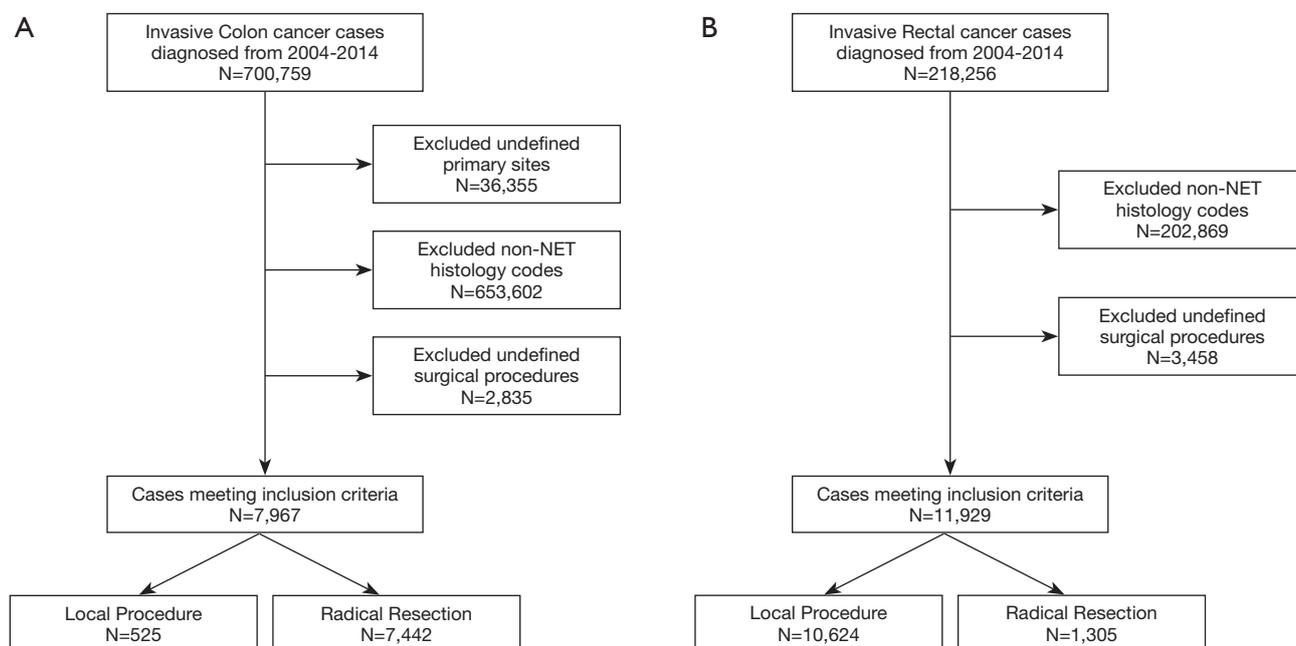


Figure 1 (A) Flow chart of inclusion/exclusion criteria among colon cancer cases. (B) Flow chart of inclusion/exclusion criteria among rectal cancer case.

analyzed. Demographic and clinical characteristics are summarized in *Table 1*. Overall, the median year of diagnosis was 2010 and the median age at diagnosis was 58 y (IQR, 47–69 y). The majority of patients were females (56.9%). Most of the patients (85.3%) were Caucasian, with 12.3% African American, and 2.3% of another racial group. Private insurance (54.1%) and Medicare (34.6%) were the most frequent payer types, although 6.2% of patients had Medicaid, and 4.1% were uninsured. The proportion of patients whose community's median income of \$63,000 or greater was 35.4%, and 16.1% had a median income of less than \$38,000. Additionally, 26.7% of patients resided in communities in which less than 7% residents had no high school degree and 14.5% in communities where the percentage with no high school degree was 21% or more. The majority of patients (86.3%) resided in metro areas, with 11.9% in urban areas, and only 1.7% in rural areas.

The majority of patients (78.9%) had no comorbidities, 16.3% had a Charlson-Deyo Score of 1, and 4.8% with a score of 2 or higher. The clinical stage of the colon tumor was Stage 0 in 0.7% of cases, Stage 1 in 33.4%, Stage 2 in 16.7%, Stage 3 in 18.6%, and Stage 4 in 30.7%. The primary colon tumor was T0 in 5.2%, T1 in 37.3%, T2 in 15.2%, T3 in 29.3%, and T4 in 13.1% of cases. Nodal involvement was absent in 76.7% of colon tumors, N1 in

18.6%, and N2 in 4.7%. Distant metastasis was present in 11.6% of colon tumors. The majority (93.4%) of colon NETs underwent radical resection, with residual tumor present in 11.9%. The median number of regional lymph nodes examined was 13 (IQR, 3–19); 66.9% of patients with nodes examined had positive nodes with a median number of 4 (IQR, 2–7) nodes positive.

Rectal NETs

A total of 11,929 rectal NETs were identified and analyzed. Demographic and clinical characteristics are also summarized in *Table 1*. Overall, the median year of diagnosis was 2010 and the median age at diagnosis was 54 y (IQR, 50–62 y). The majority of patients were females (52.8%). Most of the patients (61.0%) were Caucasian, with 29.9% African Americans, and 9.1% of another racial group. Private insurance (65.4%) and Medicare (22.1%) were the most frequent payer types, while 7.6% of patients had Medicaid, and 3.4% were uninsured. The proportion of patients with a median income of \$63,000 or greater was 32.8%, and 20.1% had a median income of less than \$38,000. Additionally, 23.1% of patients resided in communities with less than 7% percentage with no high school degree, and 20.3% in communities where the

Table 1 Demographics and clinical characteristics among neuroendocrine tumors

Characteristic	Colon (N=7,967)	Rectum (N=11,929)
Age at diagnosis		
N	7,967	11,929
Mean (SD)	57.0 (16.7)	55.4 (11.6)
Median	58.0	54.0
Q1, Q3	47.0, 69.0	50.0, 62.0
Range	(18.0–90.0)	(18.0–90.0)
Sex		
Male	3,430 (43.1%)	5,632 (47.2%)
Female	4,537 (56.9%)	6,297 (52.8%)
Race		
Missing	86	287
White	6,726 (85.3%)	7,106 (61.0%)
Black	970 (12.3%)	3,477 (29.9%)
Other	185 (2.3%)	1,059 (9.1%)
Spanish/Hispanic origin		
Missing	449	799
Non-Hispanic/Non-Spanish	7,159 (95.2%)	10,191 (91.6%)
Hispanic/Spanish	359 (4.8%)	939 (8.4%)
Charlson-Deyo Score		
0	6,287 (78.9%)	10,147 (85.1%)
1	1,299 (16.3%)	1,431 (12.0%)
2+	381 (4.8%)	351 (2.9%)
Primary payer		
Missing	123	218
No insured	324 (4.1%)	395 (3.4%)
Private insurance	4,241 (54.1%)	7,657 (65.4%)
Medicaid	483 (6.2%)	887 (7.6%)
Medicare	2,715 (34.6%)	2,584 (22.1%)
Other government	81 (1.0%)	188 (1.6%)
Percent no high school degree		
Missing	77	81
21% or more	1,143 (14.5%)	2,401 (20.3%)
13% to 20.9%	1,961 (24.9%)	3,128 (26.4%)
7% to 12.9%	2,680 (34.0%)	3,577 (30.2%)

Table 1 (Continued)**Table 1** (Continued)

Characteristic	Colon (N=7,967)	Rectum (N=11,929)
Less than 7%	2,106 (26.7%)	2,742 (23.1%)
Median income quartiles		
Missing	82	86
Less than \$38,000	1,272 (16.1%)	2,378 (20.1%)
\$38,000 to \$47,999	1,691 (21.4%)	2,547 (21.5%)
\$48,000 to \$62,999	2,129 (27.0%)	3,034 (25.6%)
\$63,000+	2,793 (35.4%)	3,884 (32.8%)
Urban/rural		
Missing	248	380
Metro	6,664 (86.3%)	10,425 (90.3%)
Urban	921 (11.9%)	1,000 (8.7%)
Rural	134 (1.7%)	124 (1.1%)
Year of diagnosis		
N	7,967	11,929
Mean (SD)	2,009.8 (3.2)	2,009.5 (3.1)
Median	2,010.0	2,010.0
Q1, Q3	2,007.0, 2,013.0	2,007.0, 2,012.0
Range	(2,004.0–2,014.0)	(2,004.0–2,014.0)
Clinical stage		
Missing	5,201	7,318
Stage 0	18 (0.7%)	46 (1.0%)
Stage 1	923 (33.4%)	4,106 (89.0%)
Stage 2	461 (16.7%)	202 (4.4%)
Stage 3	514 (18.6%)	119 (2.6%)
Stage 4	850 (30.7%)	138 (3.0%)
Clinical T Stage		
Missing	5,601	7,333
T0	123 (5.2%)	59 (1.3%)
T1	882 (37.3%)	4,101 (89.2%)
T2	359 (15.2%)	236 (5.1%)
T3	693 (29.3%)	157 (3.4%)
T4	309 (13.1%)	43 (0.9%)
Clinical N Stage		
Missing	3,963	5,981
N0	3,071 (76.7%)	5,767 (97.0%)

Table 1 (Continued)

Table 1 (Continued)

Characteristic	Colon (N=7,967)	Rectum (N=11,929)
N1	743 (18.6%)	155 (2.6%)
N2	190 (4.7%)	26 (0.4%)
Clinical M Stage		
Missing	555	719
M0	6,555 (88.4%)	11,069 (98.7%)
M1	857 (11.6%)	141 (1.3%)
Surgical procedure type		
Local	525 (6.6%)	10,624 (89.1%)
Radical resection	7,442 (93.4%)	1,305 (10.9%)
Surgical margins		
Missing	271	2,234
No residual tumor	6,777 (88.1%)	8,469 (87.4%)
Residual tumor	919 (11.9%)	1,226 (12.6%)
Number of regional lymph nodes examined		
N	7,785	11,589
Mean (SD)	13.2 (11.5)	1.0 (4.8)
Median	13.0	0.0
Q1, Q3	3.0, 19.0	0.0, 0.0
Range	(0.0–90.0)	(0.0–90.0)
Number of positive nodes (among those with at least 1 positive node)		
N	4,123	426
Mean (SD)	5.5 (5.5)	6.2 (9.4)
Median	4.0	3.0
Q1, Q3	2.0, 7.0	2.0, 7.0
Range	(1.0–78.0)	(1.0–88.0)

percentage with no high school degree was 21% or more. The majority of patients (90.3%) resided in metro areas, with 8.7% in urban areas, and only 1.1% in rural areas.

The majority of rectal NETs were clinical Stage 1 (89.0%). Other clinical stages included Stage 0 in 1.0%, Stage 2 in 4.4%, Stage 3 in 2.6%, and Stage 4 in 3.0%. The primary rectal tumor was T0 in 1.3% of patients, T1 in 89.2%, T2 in 5.1%, T3 in 3.4%, and T4 in 0.9%. Nodal involvement was absent in 97.0% of rectal tumors, N1 in 2.6%, and N2 in 0.4%. Distant metastasis was present

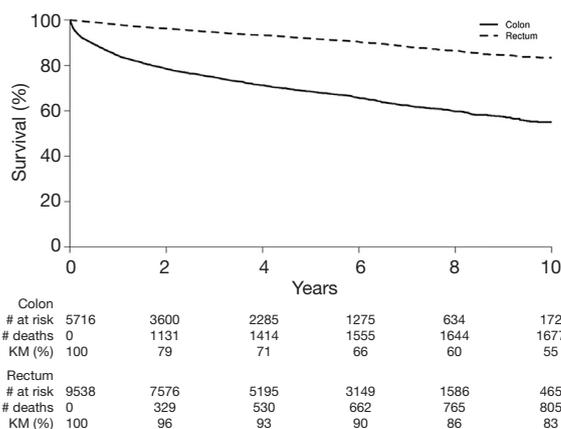


Figure 2 Overall survival for colorectal NETs.

in only 1.3% of rectal tumors. The majority (89.1%) of rectal NETs underwent local resection, with residual tumor present in 12.6%. The majority of rectal NETs did not have lymph nodes examined. Of those who had at least 1 nodes examined, 53.1% had positive nodes with a median number of 3 (IQR, 2–7) positive lymph nodes.

OS

Figure 2 shows the OS for colon and rectal NET patients respectively. The 5- and 10-year OS for colon NETs were 69% and 55% respectively. OS for rectal NETs was 92% at 5 years and 83% at 10 years.

Factors associated with radical versus local resection for NETs

On multivariable logistic regression modeling for tumor type (Table 2), an older age (OR 1.45, CI 1.37–1.53) was associated with higher odds for radical resection in colon NETs. Patients who had primary colon tumor with clinical Stage 2 (OR 3.83, CI 2.30–6.37), Stage 3 (OR 8.19, CI 3.96–16.92), and Stage 4 (OR 9.91, CI 4.56–21.52) had greater odds for radical resection than those with Stage 1 disease. Treatment with chemotherapy (OR 6.28, CI 3.32–11.88) was associated with significantly higher odds of radical resection for colon NETs than absence of chemotherapy.

For patients with rectal NETs, African American patients (OR 0.75, CI 0.64–0.88) had lower odds of radical resection than Caucasians. Patients with clinical Stage 3 had the highest odds of radical resection (OR 44.78, CI

Table 2 Multivariable logistic regression analysis of factors associated with radical versus local resection among neuroendocrine tumors

Variable	Colon multivariable OR (95% CI)	P value	Rectum multivariable OR (95% CI)	P value
Age (per 10 years)	1.45 (1.37, 1.53)	<0.001	1.05 (1.0, 1.11)	0.068
Sex				
Male	1.06 (0.88, 1.28)	0.547	1.05 (0.92, 1.19)	0.466
Female	1.0 reference		1.0 reference	
Race		Overall 0.157		Overall 0.007
White	1.0 reference		1.0 reference	
Black	1.36 (0.99, 1.87)	0.058	0.75 (0.64, 0.88)	<0.001
Other	1.25 (0.69, 2.28)	0.469	0.91 (0.73, 1.14)	0.423
Unknown	0.69 (0.34, 1.42)	0.314	0.90 (0.59, 1.35)	0.604
Median income quartiles		Overall 0.628		Overall 0.411
Less than 38,000	1.11 (0.83, 1.49)	0.482	0.84 (0.69, 1.03)	0.087
38,000–47,999	0.87 (0.68, 1.12)	0.278	0.95 (0.79, 1.13)	0.535
48,000–62,999	1.02 (0.80, 1.29)	0.880	0.99 (0.84, 1.17)	0.913
63,000+	1.0 reference		1.0 reference	
Unknown	0.90 (0.32, 2.58)	0.847	1.26 (0.65, 2.45)	0.498
Clinical stage group		Overall <0.001		Overall <0.001
Stage 0	1.39 (0.31, 6.19)	0.670	1.47 (0.58, 3.72)	0.416
Stage 1	1.0 reference		1.0 reference	
Stage 2	3.83 (2.30, 6.37)	<0.001	6.12 (4.37, 8.58)	<0.001
Stage 3	8.19 (3.96, 16.92)	<0.001	44.78 (24.49, 81.88)	<0.001
Stage 4	9.91 (4.56, 21.52)	<0.001	10.17 (6.72, 15.39)	<0.001
Unknown	2.72 (2.20, 3.35)	<0.001	1.36 (1.18, 1.57)	<0.001
Any chemotherapy		Overall <0.001		Overall <0.001
No	1.0 reference		1.0 reference	
Yes	6.28 (3.32, 11.88)	<0.001	13.17 (9.76, 17.77)	<0.001
Unknown	1.53 (0.96, 2.45)	0.077	1.34 (1.02, 1.78)	0.039

OR, odds ratio; CI, confidence interval.

24.49–81.88). Also, clinical Stage 2 (OR 6.12, CI 4.37–8.58) or Stage 4 (OR 10.17, CI 6.72–15.39), or treatment with chemotherapy (OR 13.17, CI 9.76–17.77) were associated with higher odds of radical resection for rectal NETs.

Factors associated with mortality for NETs

On multivariable Cox proportional hazard modeling for tumor type (Table 3), radical resection (OR 1.70, CI 1.18–2.45), treatment with any chemotherapy (OR 2.31, CI 2.07–

2.57), Stage 3 disease (OR 1.55, CI 1.12–2.15) or Stage 4 disease (OR 4.97, CI 3.72–6.62), lower median income quartiles (OR 1.41, CI 1.21–1.64 for less than \$38,000), and an older age (OR 1.64, CI 1.57–1.70) were associated with higher mortality for colon NETs.

Radical resection (OR 2.47, CI 2.06–2.97), treatment with any chemotherapy (OR 4.30, CI 3.34–5.55), lower median income quartiles (OR 1.72, CI 1.39–2.13 for less than \$38,000), and an older age (OR 1.88, CI 1.77–2.00) were also associated with higher odds of death from

Table 3 Multivariable cox proportional hazards regression analysis of factors associated with death among neuroendocrine tumors

Variable	Colon multivariable, OR (95% CI)	P value	Rectum multivariable, OR (95% CI)	P value
Age (per 10 years)	1.64 (1.57, 1.70)	<0.001	1.88 (1.77, 2.00)	<0.001
Sex				
Male	1.09 (0.99, 1.20)	0.075	1.34 (1.16, 1.54)	<0.001
Female	1.0 reference		1.0 reference	
Race		Overall 0.978		Overall 0.002
White	1.0 reference		1.0 reference	
Black	0.98 (0.84, 1.15)	0.841	1.26 (1.07, 1.49)	0.005
Other	0.93 (0.66, 1.32)	0.698	0.67 (0.48, 0.94)	0.021
Unknown	0.97 (0.61, 1.54)	0.891	1.03 (0.60, 1.75)	0.919
Median income quartiles		Overall <0.001		Overall <0.001
Less than 38,000	1.41 (1.21, 1.64)	<0.001	1.72 (1.39, 2.13)	<0.001
38,000–47,999	1.24 (1.09, 1.42)	0.001	1.42 (1.16, 1.74)	<0.001
48,000–62,999	1.10 (0.97, 1.25)	0.136	1.24 (1.02, 1.52)	0.032
63,000+	1.0 reference		1.0 reference	
Unknown	2.14 (1.54, 2.97)	<0.001	3.61 (2.20, 5.92)	<0.001
Clinical stage group		Overall <0.001		Overall <0.001
Stage 0	0.81 (0.11, 5.85)	0.834	4.76 (2.09, 10.85)	<0.001
Stage 1	1.0 reference		1.0 reference	
Stage 2	1.11 (0.77, 1.60)	0.588	2.20 (1.46, 3.31)	<0.001
Stage 3	1.55 (1.12, 2.15)	0.009	1.64 (1.08, 2.49)	0.021
Stage 4	4.97 (3.72, 6.62)	<0.001	8.30 (5.88, 11.72)	<0.001
Unknown	1.62 (1.23, 2.13)	<0.001	1.27 (1.05, 1.55)	0.017
Resection type				
Local	1.0 reference		1.0 reference	
Radical resection	1.70 (1.18, 2.45)	0.004	2.47 (2.06, 2.97)	<0.001
Any chemotherapy		Overall <0.001		Overall <0.001
No	1.0 reference		1.0 reference	
Yes	2.31 (2.07, 2.57)	<0.001	4.30 (3.34, 5.55)	<0.001
Unknown	1.07 (0.86, 1.33)	0.562	0.99 (0.70, 1.38)	0.935

OR, odds ratio; CI, confidence interval.

rectal tumors. Additionally, male patients (OR 1.34, CI 1.16–1.54), and African Americans (OR 1.26, CI 1.07–1.49) had higher odds of death from rectal NETs than females and Caucasians respectively. Other racial groups had lower odds of death than Caucasians (OR 0.67, CI 0.48–0.94).

Factors associated with twelve or more lymph nodes examination following radical resection

Lymph nodes were more likely to be examined during radical resection of colon NETs if the patient had clinical Stage 3 disease (OR 1.56, CI 1.16–2.10) or received

chemotherapy (OR 1.67, CI 1.44–1.94). An older age (OR 0.89, CI 0.86–0.93) and lower median income quartiles (OR 0.77, CI 0.65–0.91 for less than \$38,000) were associated with lower odds of lymph node examination in colon NET patients who underwent radical resection (Table S1). Among rectal NET patients who underwent radical resection, clinical Stage 3 (OR 2.14, CI 1.15–3.99) and Stage 4 (OR 3.15, CI 1.50–6.61) were associated with higher odds of lymph node examination.

Factors associated with short hospital stay following radical resection

Table S2 shows the factors associated with a short hospital stay following radical resection. Colon NETs patients who underwent radical resection were less likely to experience a short hospital stay if they were older (OR 0.82, CI 0.80–0.84), male (OR 0.91, CI 0.86–0.96), African Americans (OR 0.82, CI 0.75–0.90), earned lower incomes (OR 0.84, CI 0.77–0.92 for less than \$38,000), or had clinical Stage 2 (OR 0.83, CI 0.74–0.94), Stage 3 (OR 0.82, CI 0.74–0.91) or Stage 4 (OR 0.56, CI 0.50–0.62) disease. Patients with rectal NETs who underwent radical resection had lower odds of a short hospital stay if they were older (OR 0.94, CI 0.90–0.99), male (OR 0.86, CI 0.75–0.98), had clinical Stage 2 (OR 0.67, CI 0.48–0.92), Stage 3 (OR 0.48, CI 0.38–0.61) or Stage 4 (OR 0.41, CI 0.31–0.56) disease, or received chemotherapy (OR 0.75, CI 0.62–0.91).

Discussion

This study sought to identify patient level factors associated with radical versus local resection for colon and rectal NETs, and to determine how these factors influence patient outcomes following resection in a national cohort of patients. We found that a significant proportion (93%) of colon NET patients underwent radical resection while the majority of those with rectal NETs (89%) underwent local resection. Patients with advanced clinical stage disease, or those treated with any chemotherapy had significantly higher odds of undergoing radical resection regardless of tumor site. Radical resection, African American race, advanced disease, chemotherapy, low income or old age were associated with a significantly higher mortality. Finally, African Americans and low-income patients were also more likely to experience a longer hospital stay following a radical resection.

Interestingly, age was an important determinant of

incidence and mortality from colorectal NETs in our study. The median age of incidence for colon NETs in our study was 58 and 54 years in the rectal NETs. The higher incidence of colon NETs, which are more likely to be high grade, in addition to other possible co-existent comorbidities likely explain the higher mortality observed in older populations from colorectal NETs. Similar to our study, Reeders *et al.* found an older age (>65 years) to be associated with an increased risk for NET related mortality (20). Scherübl and colleagues reported a similar observation for pancreatic NETs (21).

In a recent large population based national study in the US, the proportion (89%) of rectal NET patients with tumors <2 cm who underwent local resection was similar to what we found (4). The aforementioned study demonstrated that early-stage tumors without aggressive biologic characteristics (e.g., large tumor size, early nodal involvement or poor histologic differentiation) could be preferably treated with local resection due to increased morbidity and mortality associated with radical resection similar to our findings (4). In contrast, the vast majority of colon NETs are discovered at an advanced stage [as high grade NETs or as neuroendocrine carcinomas (NECs)] and a more aggressive treatment with radical resection is recommended (13). Unsurprisingly, the majority (93%) of colon NETs in our study were treated with radical resection. Additionally, we found that the OS for colon NETs (69% at 5 y and 55% at 10 y) was significantly lower than survival for their rectal counterparts (92% at 5 y and 83% at 10 y), likely due to the increased aggressiveness of colon NETs. Although the survival rates observed in our study are similar to the rates reported by recent retrospective cohort studies (2,4,6,10,16,22), they are significantly higher than those observed in the 1990s or earlier (3,5,13,14). Scherübl *et al.* observed a 20% increase in the overall 5-year survival of patients with rectal NETs during a 35-year study period in the US (9). The improvement in survival may represent advances in diagnostic technology, earlier diagnosis and increased awareness about colorectal NETs compared to previous decades. Increasing the proportion of colon NETs diagnosed early through screening colonoscopy therefore could potentially improve OS even further.

The clinicopathologic characteristics that influence outcomes for colorectal NETs are well documented. Clinicopathologic characteristics such as tumor size, tumor depth, and lymphatic involvement have been identified as important determinants of treatment choice for colorectal NETs (15,23). The aforementioned studies demonstrated

that the larger sized neoplasms and those with lymphatic invasion would require radical resection for optimal management. Our study emphasizes the importance of the interplay between patient demographics and clinical characteristics in determining treatment patterns and patient outcomes. Interestingly, our study suggests that older patients are more likely to undergo radical resection. This is likely due to a higher prevalence of these tumors in the older population. Based on the findings of our study, colon NETs were diagnosed later in life on average than their rectal counterparts and were associated with a higher proportion of advanced disease and were more likely to undergo a radical resection. These findings are likely explained by the pathologic attributes of these tumors which tend to be larger, with a poorer differentiation or higher malignant potential than rectal NETs, thus necessitating radical resection (8,14).

Furthermore, although rectal NETs are less aggressive and exhibit a more favorable prognosis (3-5), we found that they have a higher mortality in African American or male patients than White or female patients. In another large population based study which analyzed patient data in the Surveillance, Epidemiology, and End Results (SEER) Database, the age-adjusted incidence rates of NETs for all sites were highest in African American males (4.48 per 100,000 population per year) (5). Modlin *et al.* found that rectal NETs were over-represented among African American and Asian populations within the US, suggesting a possible role of genetics in the development of the disease (5). The high disease burden in African American male population may partly account for the proportionally higher rates of death in this population, but the reasons are not completely understood. Further research to investigate genetic or pathophysiologic pathways are therefore needed. African Americans and low income patients were also more likely to experience a longer hospital stay following radical resection for colon NETs, suggesting that socially deprived individuals may experience worse outcomes as compared to the others.

There is a paucity of data regarding the role of chemotherapy and its impact on patient outcomes for colorectal NETs. Although resection is the treatment of choice in patients who can tolerate an operation and who have operable disease, chemotherapy is an option for treatment of metastatic disease (24). We found that chemotherapy treatment was associated with higher rates of radical resection for both colon and rectal NETs. This is likely explained by the presence of a coexistent advanced

(i.e., high grade NETs or poorly differentiated NECs) or metastatic disease in patients undergoing radical resection. We also found that the receipt of chemotherapy was associated with increased mortality from colorectal NETs regardless of site, and increased hospital length of stay following radical resection for rectal NETs. These findings are possibly due to the baseline severity of the disease as previously discussed, although the role other factors or mechanisms that have not been established by this study cannot be discounted.

Our study is novel for demonstrating the interplay between patient social, racial and clinical characteristics in influencing treatment modality as well as patient outcomes for colorectal NETs. Although the clinicopathologic characteristics that determine treatment choice and outcomes are extensively studied, differences in treatment and patient outcomes based on patient social and racial characteristics are not well established. Overall, our study suggests that social and racial characteristics such as age, gender, race and income are important determinants of treatment type and outcomes for colorectal NETs. These findings are strengthened by the use of a large national cancer database which increases the generalizability to the general population. There are important limitations to the study as well. The majority of the patients included in our study were from metro areas and therefore, this limits the generalizability of our study to rural-based populations. The retrospective nature of our study limits our interpretations to associations since no causal relationship can be established. For example, it is unclear if factors outside the scope of this study such as genetic or pathophysiologic mechanisms account for the worse outcomes demonstrated among racial minority such African Americans. The terminology and classification of NETs have evolved during the analyzed period of this study by the WHO 2017 NET classification. Due to the retrospective nature of this study, available data was used without reassessing the pathology specimen. This could have resulted in misclassified lesions. A significant number of cases were excluded (*Figure 1A,B*) due to undefined surgical procedures (i.e., local versus radical resections). It is unclear if excluded cases differ significantly from the cases analyzed in terms of social or demographic characteristics and outcomes. The TNM staging were not consistently documented for all patients in the database leading to a high rate of missing data for tumor staging. These patients were however included in the study due to availability of other data pertinent to the study objectives. The retrospective design also limits our ability

to account for all possible factors that influence the choice of treatment and patient outcomes for our cohort. The study has not accounted for the modulating effect of factors external to the patient such as differences in treatment outcomes among hospital and case volumes. While these factors are important, our study focused on defining the patient social and demographic factors associated with treatment and outcomes for colorectal NETs.

Conclusions

Multiple factors influence the treatment and outcomes for patients with colorectal NETs. Clinicopathologic characteristics such as tumor size, tumor depth and lymphatic invasion are well documented determinants. The social and demographic factors that influence treatment and patient outcomes have not been adequately studied. We demonstrated that patient age, gender, race and income are important social and demographic determinants of treatment and outcomes in addition to clinicopathologic characteristics. Of note, older patients are more likely to undergo radical resection, while racial minority and low-income patients experience worse outcomes following resection.

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Footnote

Reporting Checklist: The authors present the study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist. Available at: <http://dx.doi.org/10.21037/jgo-20-193>

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Conflicts of Interest: All authors have completed the ICJME uniform disclosure form (available at: <http://dx.doi.org/10.21037/jgo-20-193>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was exempt from IRB review and patients' informed-consent due to its use of de-identified data.

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Supplementary

Table S1 Multivariable logistic regression analysis of factors associated with 12+ lymph nodes examined among neuroendocrine tumors who underwent radical resection*

Variable	Colon multivariable, OR (95% CI)	P value	Rectum multivariable, OR (95% CI)	P value
Age (per 10 years)	0.89 (0.86, 0.93)	<0.001	0.94 (0.84, 1.06)	0.316
Sex				
Male	0.92 (0.83, 1.03)	0.159	0.93 (0.68, 1.27)	0.659
Female	1.0 reference		1.0 reference	
Race		Overall 0.405		Overall 0.562
White	1.0 reference		1.0 reference	
Black	0.89 (0.75, 1.05)	0.160	1.11 (0.74, 1.66)	0.619
Other	0.82 (0.56, 1.20)	0.296	1.60 (0.83, 3.09)	0.164
Unknown	1.01 (0.58, 1.79)	0.964	1.15 (0.37, 3.55)	0.813
Median income quartiles		Overall 0.024		Overall 0.338
Less than 38,000	0.77 (0.65, 0.91)	0.003	0.96 (0.58, 1.59)	0.881
38,000–47,999	0.83 (0.71, 0.97)	0.017	0.67 (0.43, 1.03)	0.070
48,000–62,999	0.93 (0.80, 1.07)	0.322	0.76 (0.50, 1.15)	0.195
63000+	1.0 reference		1.0 reference	
Unknown	0.87 (0.52, 1.47)	0.604	0.61 (0.18, 2.12)	0.441
Clinical stage group		Overall <0.001		Overall <0.001
Stage 0	2.38 (0.52, 10.94)	0.267	0.31 (0.03, 3.16)	0.325
Stage 1	1.0 reference		1.0 reference	
Stage 2	1.36 (0.99, 1.85)	0.056	1.80 (0.91, 3.56)	0.091
Stage 3	1.56 (1.16, 2.10)	0.003	2.14 (1.15, 3.99)	0.017
Stage 4	1.06 (0.82, 1.39)	0.652	3.15 (1.50, 6.61)	0.003
Unknown	0.95 (0.77, 1.18)	0.665	1.02 (0.65, 1.60)	0.934
Any chemotherapy		Overall <0.001		Overall 0.712
No	1.0 reference		1.0 reference	
Yes	1.67 (1.44, 1.94)	<0.001	1.01 (0.69, 1.47)	0.981
Unknown	1.10 (0.86, 1.40)	0.446	1.34 (0.67, 2.67)	0.414

*, among patients with at least 1 node examined. OR, odds ratio; CI, confidence interval.

Table S2 Multivariable cox proportional hazards regression analysis of factors associated with short los among neuroendocrine tumors who underwent radical resection

Variable	Colon multivariable, OR (95% CI)	P value	Rectum multivariable, OR (95% CI)	P value
Age (per 10 years)	0.82 (0.80, 0.84)	<0.001	0.94 (0.90, 0.99)	0.030
Sex				
Male	0.91 (0.86, 0.96)	0.001	0.86 (0.75, 0.98)	0.027
Female	1.0 reference		1.0 reference	
Race		Overall <0.001		Overall 0.735
White	1.0 reference		1.0 reference	
Black	0.82 (0.75, 0.90)	<0.001	0.91 (0.76, 1.09)	0.312
Other	0.83 (0.68, 1.00)	0.052	1.05 (0.81, 1.36)	0.729
Unknown	0.86 (0.66, 1.13)	0.281	0.99 (0.63, 1.55)	0.967
Median income quartiles		Overall <0.001		Overall 0.461
Less than 38,000	0.84 (0.77, 0.92)	<0.001	0.88 (0.71, 1.10)	0.266
38,000–47,999	0.88 (0.81, 0.95)	0.001	0.84 (0.69, 1.01)	0.066
48,000–62,999	0.92 (0.85, 0.99)	0.021	0.91 (0.76, 1.08)	0.282
63,000+	1.0 reference		1.0 reference	
Unknown	0.77 (0.59, 1.00)	0.054	0.91 (0.49, 1.68)	0.759
Pathologic stage group		Overall <0.001		Overall <0.001
Stage 0	1.16 (0.53, 2.58)	0.708	0.46 (0.20, 1.02)	0.057
Stage 1	1.0 reference		1.0 reference	
Stage 2	0.83 (0.74, 0.94)	0.003	0.67 (0.48, 0.92)	0.014
Stage 3	0.82 (0.74, 0.91)	<0.001	0.48 (0.38, 0.61)	<0.001
Stage 4	0.56 (0.50, 0.62)	<0.001	0.41 (0.31, 0.56)	<0.001
Unknown	0.78 (0.71, 0.86)	<0.001	0.91 (0.76, 1.09)	0.301
Any chemotherapy		Overall 0.416		Overall 0.007
No	1.0 reference		1.0 reference	
Yes	0.96 (0.88, 1.03)	0.257	0.75 (0.62, 0.91)	0.003
Unknown	1.03 (0.91, 1.17)	0.599	1.09 (0.80, 1.49)	0.574