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Interaction of Race and Pathology for Neuroendocrine Tumors: Epidemiology, Natural History, or Racial Disparity?

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Running Head: Race and Pathology in GEP-NETs

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Synopsis

Black patients with GEP-NETs have an improved 5-year recurrence-free survival compared to White patients despite having more adverse clinicopathologic characteristics. This is likely attributed to differences in primary tumor site and variable prognostic value of lymph node positivity.

Abstract

Background and Objectives: Although minority race has been associated with worse cancer outcomes, the interaction of race with pathologic variables and outcomes of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is not known.

Methods: Patients from the US Neuroendocrine Study Group (2000-16) undergoing curative-intent resection of GEP-NETs were included. Given few patients of other races, only Black and White patients were analyzed.

Results: 1143 patients were included. Median age was 58years, 49% were male, 14% Black, and 86% White. Black patients were more likely to be uninsured (7%vs.2%,p=0.011), and to have symptomatic bleeding(13%vs.7%,p=0.009), emergency surgery(7%vs.3%,p=0.006), and positive lymph nodes(LN)(47%vs.36%,p=0.021). However, Black patients had improved 5-year recurrence-free survival(RFS)(90%vs.80%, p=0.008). Quality of care was comparable between races, seen by similar LN yield, R0 resections, post-operative complications, and need for reoperation/readmission (all p>0.05). While both races were more likely to have pancreas-NETs, Black patients had more small bowel-NETs(22%vs.13%,p<0.001). LN positivity was prognostic for pancreas-NETs(5-year RFS 67%vs.83%,p=0.001) but not for small-bowel NETs.

Conclusions: Black patients with GEP-NETs had more adverse characteristics and higher LN positivity. Despite this, Black patients have improved RFS. This may be attributed to the epidemiologic differences in the primary site of GEP-NETs and variable prognostic value of LN positive disease.

KeyWords

Neuroendocrine tumors, racial disparities, lymph node positivity, small bowel, pancreas

Introduction

Although the majority are non-functional, neuroendocrine tumors are a heterogeneous group of cancers that can cause varied and non-specific symptoms from the release of hormones.[1,2] They are most commonly found in the gastrointestinal system,

but can also be present in the pancreas, lungs, thyroid, ovaries, pituitary, and adrenal glands.[1] Management includes surgical excision, which can be curative for localized disease, as well as surgical cytoreduction, radiotherapy, embolization, chemotherapy, and somatostatin analogues for patients with advanced disease.[3] For the purpose of treatment and research, gastroenteropancreatic (GEP) neuroendocrine tumors are often grouped together.[4] The most common locations of GEP neuroendocrine tumors are the small bowel and pancreas.[1,5-7] While they both have similar management strategies, the prognosis of small bowel and pancreatic neuroendocrine tumors differs.[1,8,9]

There is a large body of research regarding racial disparities in cancer outcomes and treatments, but a relatively small amount specific to neuroendocrine tumors. Available data have shown that minority race and lower socioeconomic status are associated with not only more advanced stage at diagnosis, but also with variations in treatment received and differences in outcome for neuroendocrine tumors.[1,5,10,11]

Dasari and colleagues found that Black patients with pancreatic neuroendocrine tumors had more advanced disease at diagnosis, limited utilization of surgery, and decreased disease-specific survival compared to patients of other races.[5] Zhou and colleagues likewise reported decreased overall and disease-specific survival for localized pancreatic neuroendocrine tumors in Black patients.[11] In contrast, St. Julien and colleagues found that socioeconomic status and insurance coverage, but not race, were associated with variations in treatment and survival in patients with non-metastatic pancreatic neuroendocrine tumors.[10]

Most treatment and outcome disparities research for neuroendocrine tumors has been conducted by utilizing the Surveillance, Epidemiology, and End Results (SEER) database and National Cancer Database (NCDB), and largely focuses on pancreatic neuroendocrine tumors.[5,10,11] Our aim was to investigate the interaction of race with clinicopathologic variables, disease presentation, treatment patterns, and recurrence-free survival (RFS) in GEP neuroendocrine tumors in a large multi-institutional database.

Methods

The United States Neuroendocrine Tumor Study Group (US NET-SG) is comprised of eight geographically diverse academic institutions: Emory University, University of Michigan, The Ohio State University, Stanford University, Vanderbilt University, Virginia Mason, Washington University, and University of Wisconsin. Institutional Review Board (IRB) approval was obtained at each study site prior to data collection. All patients who underwent resection for a neuroendocrine tumor from 2000-2016 were evaluated. A review of electronic medical records was conducted and pertinent baseline intraoperative, pathologic, and post-operative outcome data were collected. Staging was based on American Joint Committee on Cancer (AJCC) 7th edition guidelines. Data regarding neoadjuvant and adjuvant therapy, disease recurrence, and survival were also recorded.

Patients who underwent curative-intent resection for primary GEP neuroendocrine tumors were included. GEP neuroendocrine tumors were defined as originating in the ampulla, appendix, duodenum, pancreas, small bowel, or stomach. Patients with other concurrent malignancy, metastatic disease, or 30-day perioperative mortality were

excluded. Due to few patients of other races, only non-Hispanic Black and non-Hispanic White patients were included in this analysis.

Statistical Analysis

SPSS version 25.0 Armonk New York Software (IBM Inc.) was used for all statistical analyses. Descriptive and comparative analyses were used for the entire study cohort. Univariate and multivariable analysis of laboratory values, pathologic findings, and clinical outcomes were performed. Chi-squared analysis was used to compare categorical variables and Student's *t*-test or one-way ANOVA was used for continuous variables, where indicated. Binary logistic and Cox regression analyses were used to compare preoperative variables with outcomes. Kaplan-Meier log rank tests were used for survival analysis. Statistical significance was predefined as $p<0.05$.

Results

Patient Population and Comparative Data by Race

Of 2182 patients in the database, 1143 met inclusion criteria. Median age was 58 years and 49% were male. Median follow-up was 36 months. Fourteen percent (n=157) of patients were Black and 86% (n=986) were White. Black patients were more likely to be female (63.2% vs. 48.8%, p=0.003) and to be uninsured (6.5% vs. 2.4%, p=0.011), to present with symptomatic gastrointestinal bleeding (12.7% vs. 6.5%, p=0.009), and to require emergency surgery (7.0% vs. 2.5%, p=0.006) (Table 1). Black patients were more likely to present with tumors originating in the small bowel (21.7% vs 12.8%, p<0.001), though pancreas neuroendocrine tumors were the most common tumor type for both races

(Table 1). Black patients were also more likely to have adverse pathologic characteristics at presentation including perineural invasion (36.1% vs 25.2%, p = 0.046), positive lymph nodes (47.3% vs 35.6%, p=0.021), and presence of multifocal tumors (13.0% vs. 4.9%, p<0.001).

The quality of surgical care received was similar between Black and White patients. There were no differences in lymph node yield at surgery (12 vs 12, p=0.804), presence of positive margins after resection (12.2% vs 14.6%, p=0.498), incidence of postoperative complications (39.7% vs 47.5%, p=0.086), need for reoperation (4.1% vs 4.4%, p=1.00), or readmission (19.1% vs 18.9%, p=1.00) in Black compared to White patients.

Comparative Data by Primary Tumor Location

Patients with small bowel primaries were older (59.7 ± 12.3 vs 56.1 ± 13.9 years, p=0.002) and more likely to be Black (21.3% vs 9.1%, p<0.001) than patients with pancreas primary tumors (Table 2). Patients with small bowel primaries were also more likely to have adverse pathologic characteristics with increased rates of lymphovascular invasion (66.7% vs 28.5%, p<0.001), perineural invasion (52.0% vs 22.2%, p<0.001) and positive lymph nodes (82.1% vs 24.5%, p<0.001). Patients with pancreatic primaries were more likely to have postoperative complications (54.9% vs 36.5%, p<0.001), in particular anastomotic leak (24.5% vs 2.1%, p<0.001). The rates of reoperation, readmission, and recurrence between the two sites were similar.

Recurrence-Free Survival

When considering the entire cohort, Black patients had improved 5-year recurrence-free survival compared to White patients (89.9% vs. 79.5%, p=0.008) (Figure 1). When examining small bowel neuroendocrine tumor recurrence-free survival by race and stratifying by lymph node status, there was no significant difference in 5-year recurrence-free survival in Black and White races (lymph node negative p=0.540, lymph node positive p=0.388, Figure 2a). However, for pancreatic neuroendocrine tumors there was a significant difference in 5-year recurrence-free survival in lymph node negative tumors by Black and White races (100% vs. 81.7%, p=0.013, Figure 2b), while 5-year recurrence-free survival remained comparable by race in lymph node positive disease (68.6% vs 67.0%, p=0.960, Figure 2b). When assessing the prognostic value of lymph node positive disease, regardless of race, on Cox regression analysis, lymph node positivity was not predictive of recurrence-free survival in small bowel neuroendocrine tumors (Table 3a). Lymph node positivity, however, was associated with decreased recurrence-free survival in pancreatic neuroendocrine tumors (HR: 1.99, 95% CI: 1.30-3.06; p=0.002, Table 3b).

Discussion

Black patients undergoing surgery for curative intent resection of gastroenteropancreatic neuroendocrine tumors presented with more advanced pathologic characteristics compared to White patients. Although there may be delays in Black patients seeking or reaching care, as evidenced by these worse pathologic variables at presentation, they received similar quality of care compared to White patients at these

tertiary referral centers that comprise the US NET-SG. Despite having more advanced disease at presentation, Black patients had improved recurrence-free survival compared to White patients, suggesting that similar quality of surgical care is being offered to both races.

This is contradictory to much of the available literature regarding the impact of race on outcomes.[5,11,12] However, it is important to note that our study population is limited to patients receiving curative-intent surgical care at select academic high-volume institutions. This may in part account for racial differences in severity of disease at presentation since care was still accessed early enough to be amenable for curative-intent resection. Given our study cohort of only patients who underwent curative-intent resection, we cannot assess any potential racial disparities in the utilization of high-volume academic centers.[12]

Others in the literature that have primarily focused on race associated outcomes of pancreatic neuroendocrine tumors using SEER and NCDB data. Zhou and colleagues found that Black patients have a worse overall survival and pancreatic neuroendocrine tumor disease-specific survival, which was attributed primarily to advanced stage disease at diagnosis and decreased access to surgery.[11] More specifically, they found that there was no difference in these outcomes for Black and White patients who did undergo surgery, which corroborates our findings.[11] In another study, Fraenkel and colleagues reported that the incidence of small bowel neuroendocrine tumors was higher in Black patients compared to White patients, similar to our findings, although they found no difference in the incidence of pancreatic neuroendocrine tumors.[13]

In this study, the improved recurrence-free survival observed in Black patients may be attributed to the epidemiologic differences in the site of presentation of gastroenteropancreatic neuroendocrine tumors. Specifically, Black patients presented with a higher rate of small bowel neuroendocrine tumors than White patients. Small bowel neuroendocrine tumors generally have a better prognosis than pancreatic neuroendocrine tumors, which was present at higher rates in White patients in this study.[9] While there was not a statistically significant difference in 5-year RFS seen in this cohort, this may be due to the relatively small sample size and number of events. The impact of lymph node positivity in neuroendocrine tumors also may not be uniform across all disease sites. Our group recently reported that there is limited prognostic significance of lymph node positivity in small bowel neuroendocrine tumors if fewer than 4 lymph nodes are positive.[14] It is important to note that the average number of positive lymph nodes in this study was 3.4 and 3.8 in small bowel neuroendocrine tumors for Black and White race patients respectively. Thus, the improved recurrence-free survival observed in Black patients in the entire GEP cohort, despite a higher rate of lymph node positive disease, may be reflective of the fact that the prevalence of small bowel neuroendocrine tumors seems to be higher in Black compared to White patients, where there is limited prognostic value of lymph node positive disease. Finally, the improved survival in node negative Black patients with pancreatic neuroendocrine tumors is a relatively novel finding and will require more investigation as these numbers were small.

The generalizability of the results of this study are limited by the population, which exclusively comes from large, metropolitan, academic institutions. We were also only able to examine Black and White races due to the small sample size of other races in

the database. The small sample size of some site-specific analyses may have limited the power of the analysis. As with any retrospective study, there are concerns for selection bias and difficulty capturing complete recurrence-free survival data. Regardless, to our knowledge this represents the largest study evaluating the interaction of race with pathologic and oncologic outcomes of gastroenteropancreatic neuroendocrine tumors at centers that manage a high volume of this rare disease.

Conclusion

In contrast to published literature, in this multi-institutional study, Black patients did not have inferior outcomes from neuroendocrine tumors, and in fact had improved recurrence-free survival compared to White patients, despite presenting with more adverse pathologic characteristics. This improved recurrence-free survival seen in Black patients may be attributed to the epidemiologic differences in the site of presentation of GEP neuroendocrine tumors and the variable prognostic value of lymph node positive disease.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

Figure 1. Recurrence-Free Survival by Race

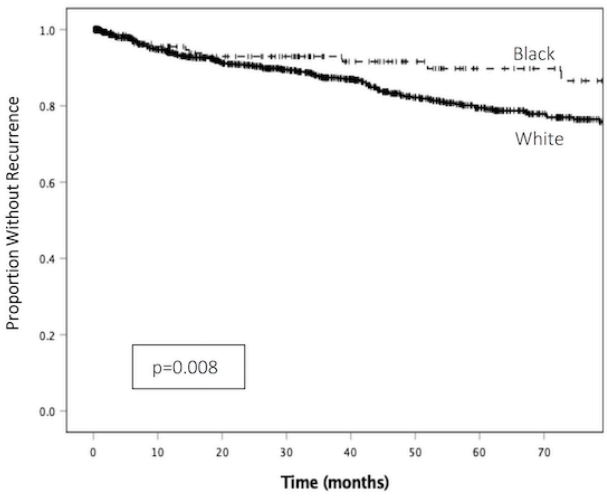

Figure 2a. Small Bowel NET Lymph Node Positivity Recurrence-Free Survival by Race

Figure 2b. Pancreatic NET Lymph Node Positivity Recurrence-Free Survival by Race

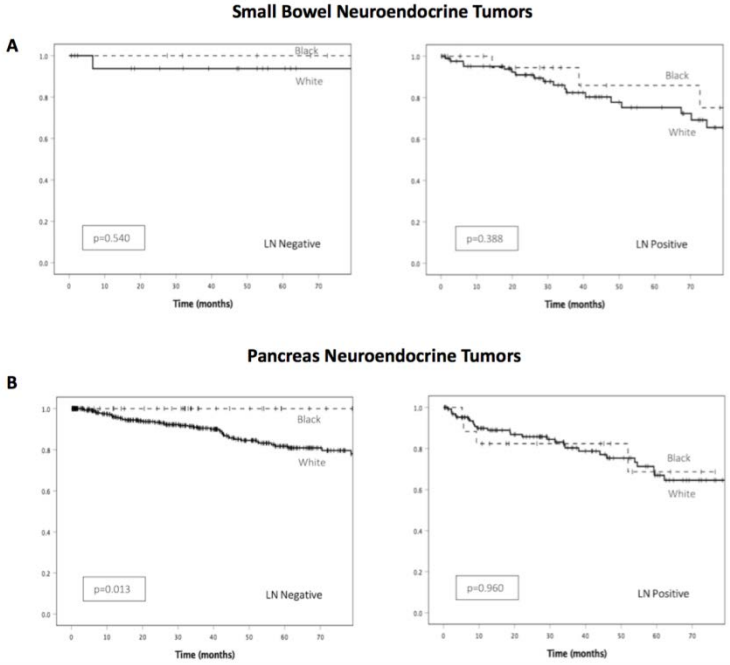

Table 1. Baseline Demographics and Presentation by Race

Variable	**White (n=986)**	**Black (n=157)**	**p-value**
Age (yrs), mean ± SD	56.7 ± 13.7	55.0 ± 14.1	0.159
Gender, n (%)			**0.003**
Male	466 (51.2)	49 (36.8)	
Female	445 (48.8)	84 (63.2)	
Health Insurance			**0.011**
Insured	950 (97.6)	145 (93.5)	
Uninsured	23 (2.4)	10 (6.5)	
Presented with GI Bleeding Event	64 (6.5)	20 (12.7)	**0.009**

Required Emergency Surgery	25 (2.5)	11 (7.0)	**0.006**
Unknown Primary at Time of Surgery	38 (3.9)	16 (10.2)	**0.001**
NET Found Incidentally	64 (6.5)	22 (14.0)	**<0.001**
Multiple Primary Tumors	40 (4.1)	1 (0.6)	0.056
Location of Tumor			**<0.001**
Pancreas	666 (67.5)	67 (42.7)	
Small Bowel	126 (12.8)	34 (21.7)	
Other GEP	194 (19.7)	56 (35.6)	
Positive Margin After Resection	142 (14.6)	19 (12.2)	**0.498**
Lymphovascular Invasion	244 (33.8)	38 (36.9)	0.617
Perineural Invasion	162 (25.5)	30 (36.1)	**0.046**
Multifocal Tumor	42 (4.9)	20 (13.0)	**<0.001**
Lymph Nodes Retrieved (yes)	271 (35.6)	52 (47.3)	0.021
Number LN Retrieved, mean ± SD	11.7 ± 9.4	12.0 ± 8.5	0.804
Positive Lymph Nodes (yes)	271 (35.6)	52 (47.3)	**0.021**
Number LN Positive, mean ± SD	1.7 ± 2.4	1.5 ± 2.6	0.570
Any Postoperative Complication	467 (47.5)	62 (39.7)	0.087
Multiple Postoperative Complications	189 (40.6)	41 (66.1)	**<0.001**
Anastomotic Leak	172 (18.6)	11 (7.5)	**0.001**

Reoperation	41 (4.4)	6 (4.1)	1.000
Readmission	185 (18.9)	30 (19.1)	1.000
Recurrence	143 (15.0)	12 (7.6)	0.019

SD, Standard Deviation; GI, Gastrointestinal, NET, Neuroendocrine

Table 2. Comparative Data by Primary Tumor Location

Variable	**Pancreas (n=733)**	**Small Bowel (n=160)**	**p-value**
Age	56.1 ± 13.9	59.7 ± 12.3	**0.002**
Gender			0.953
Male	371 (50.6)	82 (51.3)	
Female	362 (49.4)	78 (48.8)	
Race			**<0.001**
White	666 (90.9)	126 (78.8)	
Black	67 (9.1)	34 (21.3)	
Positive Margin After Resection	110 (15.1)	14 (8.9)	0.053
Lymphovascular Invasion	171 (28.5)	78 (66.7)	**<0.001**
Perineural Invasion	121 (22.2)	52 (52.0)	**<0.001**
Lymph Nodes Retrieved (yes)	615 (84.4)	142 (89.9)	0.099
Positive Lymph Nodes	151 (24.5)	119 (82.1)	**<0.001**
Any Postoperative Complication	402 (54.9)	58 (36.5)	<0.001

Multiple Postoperative Complications	169 (42.1)	22 (37.9)	0.641
Anastomotic Leak	171 (24.5)	3 (2.1)	**<0.001**
Reoperation	25 (3.6)	10 (6.9)	0.111
Readmission	169 (23.1)	27 (17.1)	0.121
Recurrence	94 (13.0)	26 (17.7)	0.168
5-year Recurrence-Free Survival			
Entire Cohort	81.1%	81.9%	0.890
White Patients Only	81.1%	79.2%	0.341
Black Patients Only	81.1%	91.1%	0.160

SD, Standard Deviation

Table 3a. Cox Regression for Recurrence-Free Survival: Small Bowel

Variable	Univariate Analysis	p-value	Multivariable Analysis	p-value
Race				
White	Reference	0.135	Reference	0.320
Black	0.397 (0.118-1.335)		0.539 (0.159-1.821)	
Lymph Node Positivity	5.040 (0.678-37.48)	0.114		

Table 3b. Cox Regression for Recurrence-Free Survival: Pancreas

Variable	Univariate Analysis	p-value	Multivariable Analysis	p-value
Race				
White	Reference	0.074	Reference	0.103
Black	0.400 (0.146-1.09)		0.433 (0.159-1.18)	
Lymph Node Positivity	1.97 (1.28-3.03)	**0.002**	1.99 (1.30-3.06)	**0.002**