Racial/Ethnic Disparities in Gastrointestinal-Neuroendocrine Tumors

Subjects: Oncology

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The impact of race and ethnicity on survival characteristics in non-pancreatic gastrointestinal tract neuroendocrine tumors is understudied. We evaluated the survival outcomes and racial/ethnic disparities in the gastrointestinal tract neuroendocrine tumors, including the esophagus, stomach, small intestine, colon, rectum, and appendix. Survival trends were determined among three groups: Hispanic, non-Hispanic White, and non-Hispanic Black. We analyzed a large national database and found that race/ethnicity is an independent prognostic factor in patients with gastrointestinal neuroendocrine tumors. Hispanic patients had better overall survival than non-Hispanic White patients, whereas non-Hispanic Black patients had favorable cause-specific survival compared to non-Hispanic White patients. This survival disparity can be attributed to differences in the site of origin, age, and stage at presentation between various race/ethnicity. Understanding these differences between race and ethnicity is needed to reduce disparities in cancer outcomes.

Keywords: neuroendocrine tumors ; gastrointestinal tract ; survival analysis ; database ; race factors

1. Introduction

Neuroendocrine tumors are rare and heterogeneous type of tumors caused by the malignant transformation of the neuroendocrine cells of many different organs [1]. Gastrointestinal neuroendocrine tumors constitute approximately 60% of all neuroendocrine tumors, with the small intestine being the most frequent site of origin, followed by the rectum, colon, and stomach [2][3]. Each anatomical location has distinct clinical, pathological characteristics, treatment response, and prognosis [4][5].

The worldwide burden of neuroendocrine tumors, and more specifically gastrointestinal tract neuroendocrine tumors, has increased over the last several decades due to increased use of diagnostic and screening studies (endoscopy, computer tomography, etc.), immunohistochemical sensitivity, and awareness in physicians [6][7]. According to Surveillance, Epidemiology, and End Results (SEER), the incidence rate of neuroendocrine tumors has increased from 1.09/100,000 to 6.9/100,000 [5][6][8][9][10], and the small intestine and rectal neuroendocrine tumors incidence rate has risen more than other gastrointestinal tract neuroendocrine tumors [11]. Besides the increased usage of diagnostic tests, other risk factors associated with the development of gastrointestinal tract neuroendocrine tumors include diet, environmental exposures, and use of profound acid suppression by proton pump inhibitors [12]. Although the annual incidence of gastrointestinal tract neuroendocrine tumors has been increasing worldwide, prognostic factors related to survival outcomes are not well described. In contrast, racial disparities have been associated with variable survival outcomes in solid malignancies, including pancreatic neuroendocrine tumor, prostate, colorectal, and female breast neoplasms [13][14][15][16][17]. To date, the impact of race and ethnicity on non-pancreatic gastrointestinal tract neuroendocrine tumors has not been well studied.

2. Discussion

This study used the SEER database to examine the largest series of patients with gastrointestinal tract neuroendocrine tumors, comparing their survival outcomes based on race/ethnicity. The current analysis is unique as it includes detailed information about the Hispanic population with gastrointestinal neuroendocrine tumors, as this group had limited information in prior reports. The result indicates that Hispanic patients had better overall survival than non-Hispanic White patients, while non-Hispanic Black patients had better cause-specific survival than non-Hispanic White patients. This difference persisted after adjusting for potential confounding factors. The lower survival in non-Hispanic White patients was observed despite increased use of surgical, radiation, and chemotherapy treatment modalities. The variables that explain these differences include the site of origin, rate of metastases at presentation, stage of the disease, and age of the non-Hispanic White population compared to the rest.

There were significant racial/ethnic differences identified in the pattern of gastrointestinal neuroendocrine tumors in the present study. The Hispanic patients were significantly younger than other ethnicities at the time of the presentation. Non-Hispanic White patients had a higher frequency of small intestine and colon neuroendocrine tumors, while non-Hispanic Black patients had a higher rate of rectal neuroendocrine tumors. Our results corroborate results from older studies that showed the small intestine neuroendocrine tumor had a higher rate of metastasis at presentation, while stomach and rectal neuroendocrine tumors were present with localized disease [18]. Similarly, colon neuroendocrine tumors had higher tumor grade and behaved more aggressively than rectal neuroendocrine tumors. Yao et al., evaluated the patients from the SEER database diagnosed between 1973 and 2004 and found that rectal neuroendocrine tumors were frequent in Black patients [19]. Hauso et al. compared the Norwegian Registry of Cancer and SEER databases for the patients with neuroendocrine tumors reported in 1993–2004 to assess the racial differences. They found that the incidence of the rectal neuroendocrine tumor was found to be three- to six-fold higher in Black patients than Caucasians [20]. The biological or genetic reasons for the racial differences in age of onset and the site of origin of the gastrointestinal neuroendocrine tumor are unknown at this time.

We then performed multivariable survival analysis to identify independent predictors of overall survival and cause-specific survival. Significant factors of survival included age, sex, race, primary tumor site, tumor histology, marital status, tumor size, previous treatments, disease stage, and tumor grade. This confirmed results from a previous analysis that showed worse cause-specific survival in gastrointestinal tract neuroendocrine tumors patients with a lack of insurance, higher tumor grade, greater tumor size, and metastatic disease [18]. With regard to the racial/ethnic differences on overall survival and cause-specific survival associated with gastrointestinal tract neuroendocrine tumors, we found that Hispanics and non-Hispanic Black patients had better survival outcomes than non-Hispanic White patients. The subgroup analysis based on the primary site showed that non-Hispanic Black patients had better cause-specific survival in the small intestine neuroendocrine tumor compared to non-Hispanic White patients. A study from the United States Neuroendocrine Tumor Study Group with a multi-institutional database reported on the effect of racial disparities on clinical outcomes in 1143 patients surgically-resected gastroenteropancreatic neuroendocrine tumors. They compared the non-Hispanic White and non-Hispanic Black patients only and did not include the Hispanic patient population. It showed better disease-free survival in non-Hispanic Black patients despite having a higher lymph node involvement [21]. Another study from Shen et al. used SEER and SEER-Medicare databases to describe racial differences in the incidence and survival of patients with all distant-stage neuroendocrine tumors. Compared to our results, the authors identified that Blacks have a higher incidence of neuroendocrine tumors and worse overall survival rate [22]. However, our study as well their data clearly show that neuroendocrine tumor is a heterogeneous disease, and site of origin plays an important role in survival outcomes. The difference was observed in that study, and our results can be attributed to our analyses focusing on non-pancreatic gastrointestinal neuroendocrine tumors, while they focused on all various types of neuroendocrine tumors, which is a heterogeneous population. Our analysis adds to the literature by assessing the impact of confounding factors on race and ethnicity. This survival disparity may be explained by genetic variations among race/ethnicity, but such information is lacking due to the low incidence of this disease [23][24].

This study has several limitations. Underreporting is a potential limitation of retrospective database studies, which might lead to selection bias. There is no patient-level socioeconomic information, and county-level information is not able to provide the socioeconomic status of the individual patients, which may have a significant effect on the patient's survival. Other clinical details such as comorbidity, family and social histories, concurrent medications, and molecular characteristics are not accessible on the SEER database, which may impact survival outcomes. Information on disease recurrence recurrent information is also unavailable.

3. Conclusions

This study suggests that race and ethnicity are important prognostic factors for survival outcomes in gastrointestinal tract neuroendocrine tumors. Hispanic patients had a more favorable overall survival rate than non-Hispanic White patients, whereas non-Hispanic Black patients had better cause-specific survival compared to non-Hispanic White patients. This survival disparity can be attributed to differences in the site of origin, age, and stage at presentation between various races/ethnicities.

References

1. Günter Klöppel; Aurel Perren; Philipp U. Heitz; The Gastroenteropancreatic Neuroendocrine Cell System and Its Tumors: The WHO Classification. *Annals of the New York Academy of Sciences* **2004**, *1014*, 13-27, 10.1196/annals.1294.002.

2. Irvin M. Modlin; Kjell Oberg; Daniel C. Chung; Robert T. Jensen; Wouter W. De Herder; Rajesh V. Thakker; Martyn Caplin; Gianfranco Delle Fave; Greg A. Kaltsas; Eric P. Krenning; et al. Gastroenteropancreatic neuroendocrine tumours. *The Lancet Oncology* **2007**, *9*, 61-72, 10.1016/s1470-2045(07)70410-2.

3. Andrea Frilling; Göran Åkerström; Massimo Falconi; Marianne Pavel; Jose Ramos; M. Kidd; Irvin Mark Modlin; Neuroendocrine tumor disease: an evolving landscape. *Endocrine-Related Cancer* **2012**, *19*, R163-R185, 10.1530/erc-12-0024.

4. Daniel M. Halperin; Chan Shen; Arvind Dasari; Ying Xu; Yiyi Chu; Shouhao Zhou; Ya-Chen Tina Shih; James C. Yao; Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *The Lancet Oncology* **2017**, *18*, 525-534, 10.1016/s1470-2045(17)30110-9.

5. Da Man; Jingjing Wu; Zhan Shen; Xiaoyi Zhu; Prognosis of patients with neuroendocrine tumor: a SEER database analysis. *Cancer Management and Research* **2018**, *10*, 5629-5638, 10.2147/cmar.s174907.

6. Mi Ri Lee; Cynthia Harris; Kiwoon Joshua Baeg; Anne Aronson; Juan P. Wisnivesky; Michelle Kang Kim; Incidence Trends of Gastroenteropancreatic Neuroendocrine Tumors in the United States. *Clinical Gastroenterology and Hepatology* **2019**, *17*, 2212-2217.e1, 10.1016/j.cgh.2018.12.017.

7. Arvind Dasari; Chan Shen; Daniel Halperin; Bo Zhao; Shouhao Zhou; Ying Xu; Tina Shih; James C. Yao; Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncology* **2017**, *3*, 1335-1342, 10.1001/jamaoncol.2017.0589.

8. Arvind Dasari; Kathan Mehta; Lauren A. Byers; Halfdan Sorbye; James. C. Yao; Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. *Cancer* **2017**, *124*, 807-815, 10.1002/cncr.31124.

9. Ron Basuroy; Raj Srirajaskanthan; J. (John) Ramage; Neuroendocrine Tumors. *Gastroenterology Clinics of North America* **2016**, *45*, 487-507, 10.1016/j.gtc.2016.04.007.

10. M. Fraenkel; M.K. Kim; A. Faggiano; G.D. Valk; Epidemiology of gastroenteropancreatic neuroendocrine tumours. *Best Practice & Research Clinical Gastroenterology* **2012**, *26*, 691-703, 10.1016/j.bpg.2013.01.006.

11. Vassiliki L. Tsikitis; Betsy C. Wertheim; Marlon A. Guerrero; Trends of Incidence and Survival of Gastrointestinal Neuroendocrine Tumors in the United States: A Seer Analysis. *Journal of Cancer* **2011**, *3*, 292-302, 10.7150/jca.4502.

12. Nina Nandy; Joshua A. Hanson; Robert G. Strickland; Denis M. McCarthy; Solitary Gastric Carcinoid Tumor Associated with Long-Term Use of Omeprazole: A Case Report and Review of the Literature. *Digestive Diseases and Sciences* **2015**, *61*, 708-712, 10.1007/s10620-015-4014-0.

13. Haichang Xin; Racial Disparity in Localized Prostate Cancer Mortality. *Journal of the National Medical Association* **2016**, *109*, 86-92, 10.1016/j.jnma.2017.01.007.

14. Christian S. Jackson; Matthew Oman; Aatish M. Patel; Kenneth J. Vega; Health disparities in colorectal cancer among racial and ethnic minorities in the United States. *Journal of Gastrointestinal Oncology* **2016**, *7*, S32-S43, 10.3978/j.issn.2078-6891.2015.039.

15. Clement G. Yedjou; Jennifer N. Sims; Lucio Miele; Felicite Noubissi; Leroy Lowe; Duber D. Fonseca; Richard A. Alo; Marinelle Payton; Paul B. Tchounwou; Health and Racial Disparity in Breast Cancer. *Advances in Experimental Medicine and Biology* **2019**, *1152*, 31-49, 10.1007/978-3-030-20301-6_3.

16. Suleyman Yasin Goksu; Muhammet Ozer; Syed Mohammad Ali Kazmi; Nina N. Sanford; Todd Aguilera; Chul Ahn; David Hsiehchen; Aravind Sanjeevaiah; Leticia Khosama; Jonathan S. Bleeker; et al. Distinct Clinical Characteristics in Young-Onset Pancreatic Neuroendocrine Tumor. *Cancers* **2020**, *12*, 2501, 10.3390/cancers12092501.

17. Huaqiang Zhou; Yuanzhe Zhang; Xiaoyue Wei; Kaibin Yang; Wulin Tan; Zeting Qiu; Si Li; Qinchang Chen; Yiyan Song; ShaoWei Gao; et al. Racial disparities in pancreatic neuroendocrine tumors survival: a SEER study. *Cancer Medicine* **2017**, *6*, 2745-2756, 10.1002/cam4.1220.

18. Wen Cai; Yinuo Tan; Weiting Ge; Kefeng Ding; Hanguang Hu; Pattern and risk factors for distant metastases in gastrointestinal neuroendocrine neoplasms: a population-based study. *Cancer Medicine* **2018**, *7*, 2699-2709, 10.1002/cam4.1507.

19. James C. Yao; Manal Hassan; Alexandria Phan; Cecile Dagohoy; Colleen Leary; Jeannette E. Mares; Eddie K. Abdalla; Jason B. Fleming; Jean-Nicolas Vauthey; Asif Rashid; et al. One Hundred Years After “Carcinoid”: Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. *Journal of Clinical Oncology* **2008**, *26*, 3063-3072, 10.1200/jco.2007.15.4377.

20. Oyvind Hauso; Bjorn I. Gustafsson Md; Mark Kidd; Helge L. Waldum Md; Ignat Drozdov; Anthony K. C. Chan; Irvin M. Modlin; Neuroendocrine tumor epidemiology. *Cancer* **2008**, *113*, 2655-2664, 10.1002/cncr.23883.

21. Danielle K. DePalo; Rachel M. Lee; Alexandra G. Lopez-Aguiar; Adriana C. Gamboa; Flavio Rocha; George Poultsides; Mary Dillhoff; Ryan C. Fields; Kamran Idrees; Hari Nathan; et al. Interaction of race and pathology for neuroendocrine tumors: Epidemiology, natural history, or racial disparity?. *Journal of Surgical Oncology* **2019**, *120*, 919-925, 10.1002/jso.25662.
22. Chan Shen; Dian Gu; Shouhao Zhou; Ying Xu; Amir Mehrvarz Sarshekeh; Daniel Halperin; Ya-Chen T. Shih; James C. Yao; Arvind Dasari; Racial Differences in the Incidence and Survival of Patients With Neuroendocrine Tumors. *Pancreas* **2018**, *48*, 1373-1379, 10.1097/mpa.0000000000001431.
23. Meganathan P. Ramakodi; Karthik Devarajan; Elizabeth Blackman Mph; Denise Gibbs Bs; Danièle Luce; Jacqueline Deloumeaux Md; Suzy Duflo; Jeffrey C. Liu; Ranee Mehra; Rob J. Kulathinal; et al. Integrative genomic analysis identifies ancestry-related expression quantitative trait loci on DNA polymerase β and supports the association of genetic ancestry with survival disparities in head and neck squamous cell carcinoma. *Cancer* **2016**, *123*, 849-860, 10.1002/cncr.30457.
24. Yutaka Hashimoto; Marisa Shiina; Taku Kato; Soichiro Yamamura; Yuichiro Tanaka; Shahana Majid; Sharanjot Saini; Varahram Shahryari; Priyanka Kulkarni; Pritha Dasgupta; et al. The role of miR-24 as a race related genetic factor in prostate cancer. *Oncotarget* **2017**, *8*, 16581-16593, 10.18632/oncotarget.15016.
