Neuroendocrine Tumors

Epidemiology of Neuroendocrine Tumors in an Eastern Caribbean nation-A Retrospective study

Shariful Islam[1] MBBS, DM, FACS, FASBrS, Shiva Chackan[1,2] MBBS, Troy Lum[1,2] MBBS, Vinoo Bheem[1] FRCS, Patrick Harnarayan[2] FRCS, FACS, Vijay Naraynsingh[2] FRCS, FACS

Affiliation:

1. San Fernando Teaching Hospital, San Fernando, Trinidad and Tobago

2. Department of Clinical Surgical Science, University of the West Indies, St Augustine, Trinidad and Tobago

***Corresponding Author**:*

Dr. Shariful Islam MBBS, DM, FACS, FASBrS

Associate Lecturer, Department of Clinical Surgical science, University of the West Indies, St Augustine, Trinidad and Tobago

Consultant Surgeon, Department of Surgery, San Fernando Teaching Hospital, San Fernando, Trinidad and Tobago

Phone: 868 797 4951. Email: sssl201198@yahoo.com / shar_islam7@hotmail.com

Abstract:

Neuroendocrine tumors are rare but increasing malignancies with a lacking data cohort in Trinidad and Tobago and the wider Caribbean. Hence the epidemiology of this cancer is largely unknown in a West Indian population. In an effort to fill this data gap a retrospective examination of all histologically confirmed NET during the 5 year period, January 1st, 2012 to December 31st, 2017 was conducted. Age, sex, tumor size, location and metastases at presentation were some of the criteria examined. Thirty-six confirmed NET were included with an average age of 54 years at diagnosis and an almost 1.5 times female preponderance for the development of NETs. Additionally, a rising incidence of almost 15 fold over the 5 year period with appendiceal tumors accounting for 31% of NETs diagnosed was noted. In direct contrast, however, small bowel tumors showed an 83% rate of metastases at presentation. The lack of comparative data highlights the requirement of further research regarding NETs in a Caribbean population.

Keywords: Neuroendocrine tumor, Epidemiology, Caribbean Population

Introduction:

Neuroendocrine tumors (NET) encompass a group of slow growing malignancies occurring in the gastrointestinal and broncho-pulmonary systems. Their origins may also lie in pancreatic, thyroid, adrenal and pituitary tissue [1-4]. The symptomatology of these particular cancers range from diarrhea, flushing, bronchospasm and cardiac valve disease are intimately related to the release of serotonin by these tumors [2].

Rarity, tumor heterogeneity, non- specific presentation symptoms contribute to delays in diagnosis [5]. However despite late presentations and significant metastatic disease at presentation [1,5], an understanding of the epidemiology is still unknown in Trinidad and Tobago or even the wider Caribbean region despite many international databases being well established [6].

This study aims to investigate the anatomical distribution as well as to determine the age and sex of patients with histologically confirmed diagnosis of neuroendocrine malignancies at our tertiary Hospital.

Design and Methods:

A retrospective study encompassing all histologically confirmed NET by the Department of Pathology at San Fernando General Hospital, irrespective of age, gender, location and co-morbid conditions between the period January 2012 to December 2017. Histological reports were obtained from the Department of Pathology Server and patient demographic data, tumor location and extent of disease obtained from the final reports.

Each report was coded and master sheet privy only to the principal investigator, hence preserving the anonymity of patients involved in this study. Ethical approval was obtained from the institutional review board to conduct the study.

Inclusion Criteria:

Any patient diagnosed and confirmed via histology with a NET during the period January 2012 and December 2017 via ACCJ 7th Edition Classification.

Exclusion Criteria: None

Data Analysis:

Data were entered into Microsoft Excel spread sheet version 2010 and analyzed by simple calculation.

Results:

During the period January 1st 2012 to December 31st 2017, 36 patients were histologically diagnosed with neuroendocrine tumors at our tertiary Hospital. A gradual rise in the incidence of these tumors was noted during this period with the 2017 accounting for the most cases diagnosed with NET representing 42% of the sample population evident in Graph 1. Average age at diagnosis was 54 years with a slightly higher ratio in males of 56.17 compared to females 52.27. Of the 36 patients encompassed in this study, 14 cases were male representing 39% with the remaining 61% being female accounting for 22 cases.

Of note appendiceal NET was the most common location of origin representing 31% due to 11 cases being diagnosed of which only 1 displayed metastatic diseases at presentation evident in Chart 1. In direct contrast however, small bowel NET, the second most common NET identified at our institution accounting for 17% revealed a 83% metastatic rate at diagnosis evident in Table 1.

Despite a 50% clear nodal status at diagnosis, a 42% T_4 tumor detection rate was found at initial surgery in these patients. While most of the NET detected in our study were well differentiated pathologically, 19% represented the poorly differentiated tumors of which all were metastatic at initial diagnosis.

Table 1: Table Showing Age, Sex, Location and Metastatic Distribution of NET

Tumor Location	Total Cases /36	Male	Female	Metastatic at Diagnosis
Appendix	11	27%	73%	9%
Right Colon	4	50%	50%	50%
Left Colon	4	50%	50%	50%
Stomach	4	50%	50%	25%
Breast	1	0%	100%	100%
Lung	1	100%	0%	100%
Gallbladder	1	100%	0%	0%
Small Bowel	7	43%	57%	83%
Pancreas	3	33%	67%	100%

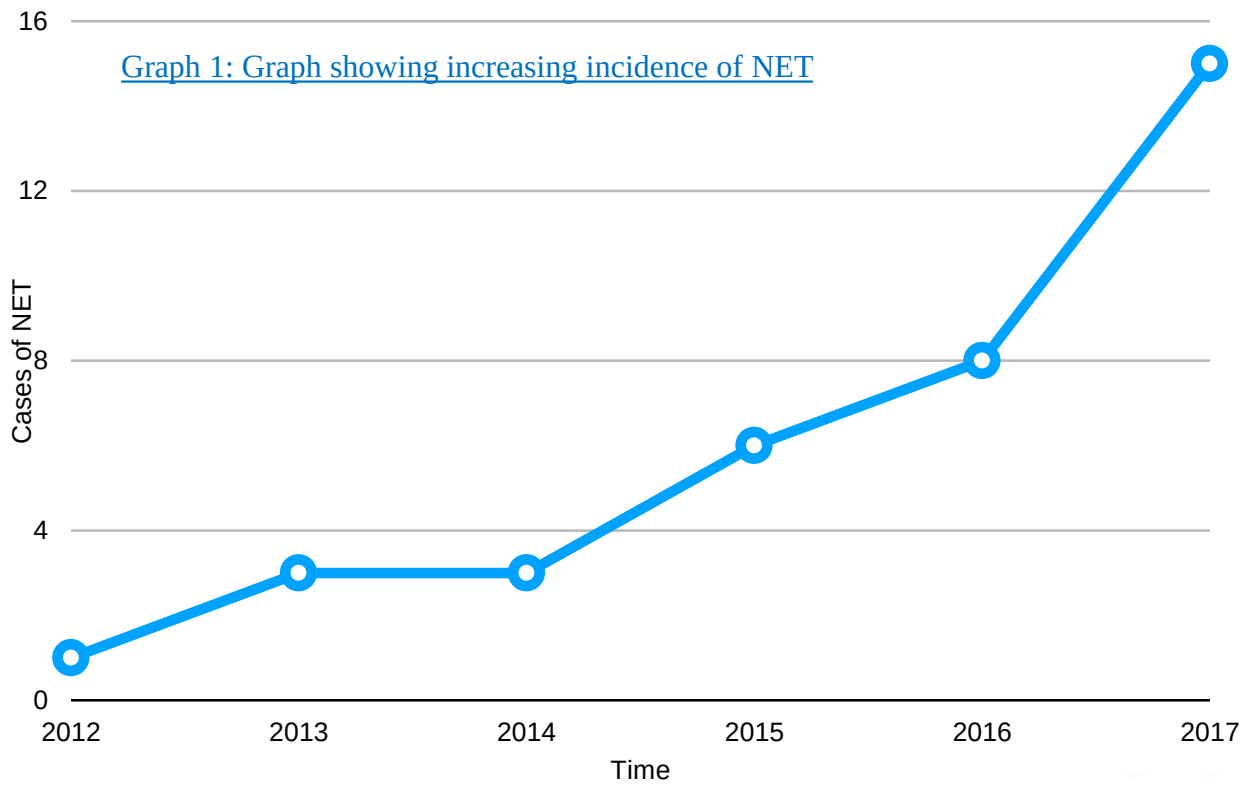
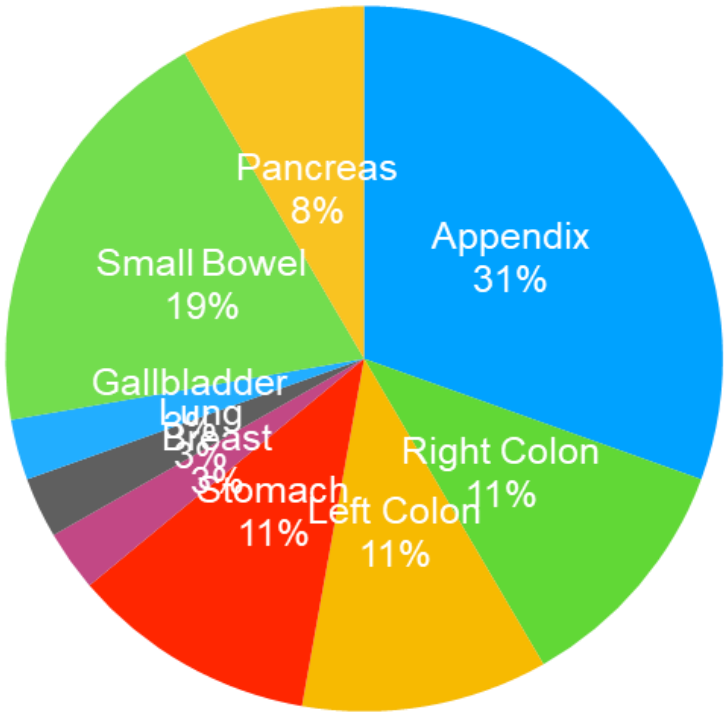


Chart 1. Pie Chart Showing Distribution of Location of Neuroendocrine Tumors



Discussion:

Neuroendocrine tumors of the diffuse neuroendocrine cell system, despite many variances share common features including growth pattern and expression of neuroendocrine markers [3]. In the examination of the published international data regarding NETs, an increasing incidence of these rare malignancies has been noted [3, 7-9]. In addition an increased female preponderance for the development of these lesions was reported [7,9,15]. However, significant age disparity was evident compared to previous data [11,16-19]. Locality of tumor origin however showed particularly variable results among various publications reviewed [14,16,18,19].

This study represents the only data regarding epidemiology of NETs at any institution in Trinidad and Tobago and the wider Caribbean. Over the 5 year examination period, a rising incidence of almost 15 fold was noted, comparable to international publications [9,15,16]. A female preponderance of almost 1.5 times was discovered compared to male patients. In addition appendiceal carcinoids were found to be the most common NET relating directly to Japanese data [18]. In direct contrast to international data however, our results showed that small bowel tumors presented almost invariably with metastatic disease [11,20].

All publications reviewed revealed increased in detection amongst their populations examined [9,10]. North American reports indicate an almost 16% increased incidence from 1995 with gastrointestinal NET accounting for the majority of increases [16,19]. Norwegian cancer registries revealed an almost 46%

increase since 1993 but cited a vast improvement in imaging for detection as a primary reason for this significant increase. Japanese populations indicated an 18% rise in detection rates of NET since 2005 [11,18]. Local incidence rates are largely unreported with the Caribbean region, having no published data. However, this study revealed a much higher rise in the incidence of these tumors of almost 15 fold over the past five years compared to international data.

The rising incidences of these NET have been widely examined internationally but regional and local data is largely absent. As such, a means for comparison regarding this rising incidence is impossible. Rising incidence of these tumors may not necessarily indicate a true increase in tumorigenesis but rather may be attributable to a number of factors including improvements in data recording and improvements, as well as increased availability of diagnostic imaging. Computed Tomography and Gastrointestinal Endoscopy, both available at our Hospital, have been suggested as explanations for increased incidental detection of asymptomatic NET internationally [6]. No study has however formally examined diagnostic imaging and their role in detection rates of NET. In addition, increased detection rates may reveal less aggressive tumors which are unlikely to become symptomatic or even diagnosed.

In the examination of disparity of distribution with respect to age and gender, mixed results were encountered based on population. Western populations noted a 1.8 versus 1.5 female to male disparity [10,16] compared to Eastern populations which showed more equivalent ratios with respect to gender [11,14,18]. Average ages in published reports regarding NET in Western populations showed 60.9 years [19] with slightly higher mean ages in Eastern populations of 63.4 years [18], a difference which may be attributable again to increased imaging in Western medicine today. Our local populations revealed an almost 10 year earlier age of diagnosis compared to international populations with our average age being represented as 54 years at initial diagnosis of these tumors with a similar female predisposition to developing NETs.

Locality of various NET also displayed much variability among examined publications with North American research showing broncho-pulmonary NET accounting for the majority, 25%, of neuroendocrine neoplasms in this region [10,19]. European research revealed small intestine being the most common tissue of origin of NET accounting for 21% [17,20]. Asian populations showed gastrointestinal particularly appendiceal tumors being the most common locality realizing up to 62% of carcinoid tumors [12-15]. The Trinidad and Tobago population showed vast similarities to the Asian population despite our more varied heritage revealing appendiceal tumors as our most common locality of neuroendocrine neoplasm.

It is acknowledged that this study has many limitations intrinsically associated with the inherent data. Firstly, this study relies on histological diagnosis which may lead to a gross underestimation of these tumors which was identified as a limitation in most international publications[16,17]. Secondly, lack of data beyond 2012 may contribute to a spurious rising incidence. In addition the small numbers examined could serve to further falsify the proportions noted. Lastly, an absence of comparative data in similar population sizes and resources available would serve to further decrease the power of this study.

However, this study provides a pilot example of the data required to improve our understanding and guide treatment, specifically catered for our Caribbean population, regarding these tumors.

Conclusion:

Despite small populations of patients histologically diagnosed with neuroendocrine tumors over the past 5 years at our Hospital, a rising incidence of these tumors is appreciated. Females were noted to be 1.5 times more likely to develop these tumors and at a younger age than their male counterparts. In addition our population showed an almost 10 year earlier age of detection of these tumors compared to international populations. In light of this data however, the absence of any comparative information

and need for further research regarding NETs became apparent.

Data availability statement: Data is embedded in the article and also kept with the corresponding author. It will be made available upon request.

Funding: No funding is received from to publish this article

Guarantor: The corresponding author will accept the full responsibility for the work.

Disclosure: The authors have nothing to disclose

Conflicts of interest: The authors declare no conflicts of interest

Acknowledgments: The authors acknowledge the contribution of the staffs at the pathology departments at our Teaching hospital for their great efforts in managing these patients.

References:

1. Yao, James C., 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*, vol. 26, no. 18, 2008.
2. Modlin, Irvin M., et al. "Current Status of Gastrointestinal Carcinoids." *Gastroenterology*, vol. 128, no. 6, 2005.
3. Modlin, Irvin M., et al. "A 5-Decade Analysis of 13,715 Carcinoid Tumors." *Cancer*, vol. 97, no. 4, Mar. 2003.
4. Modlin, Irvin M., et al. "A Three-Decade Analysis of 3,911 Small Intestinal Neuroendocrine Tumors: The Rapid Pace of No Progress." *The American Journal of Gastroenterology*, vol. 102, no. 7, 2007.
5. Modlin, Irvin M., et al. "Priorities for Improving the Management of Gastroenteropancreatic Neuroendocrine Tumors." *JNCI: Journal of the National Cancer Institute*, vol. 100, no. 18, 2008.
6. Zárate, Xeily, et al. "Pancreatic Incidentalomas." *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 26, no. 1, 2012.
7. Maggard, Melinda A., et al. "Updated Population-Based Review of Carcinoid Tumors." *Annals of Surgery*, vol. 240, no. 1, 2004.
8. Perez, Eduardo A., et al. "7201 Carcinoids: Increasing Incidence Overall and Disproportionate Mortality in the Elderly." *World Journal of Surgery*, vol. 31, no. 5, Apr. 2007.
9. Hemminki, Kari, and Xinjun Li. "Incidence Trends and Risk Factors of Carcinoid Tumors." *Cancer*, vol. 92, no. 8, 2001.
10. Price, B. "Mesothelioma Trends in the United States: An Update Based on Surveillance, Epidemiology, and End Results Program Data for 1973 through 2003." *American Journal of Epidemiology*, vol. 159, no. 2, 2004.
11. Goh, Kl. "Changing Trends in Gastrointestinal Disease in the Asia–Pacific Region." *Journal of Digestive Diseases*, vol. 8, no. 4, 2007.
12. Sandor, A. "A Retrospective Analysis of 1570 Appendiceal Carcinoids." *The American Journal of Gastroenterology*, vol. 93, no. 3, 1998.
13. Mcgory, Marcia L., et al. "Malignancies of the Appendix: Beyond Case Series Reports." *Diseases of the Colon & Rectum*, vol. 48, no. 12, 2005.
14. Ito, Tetsuhide, et al. "Preliminary Results of a Japanese Nationwide Survey of Neuroendocrine Gastrointestinal Tumors." *Journal of Gastroenterology*, vol. 42, no. 6, 2007.
15. Strosberg, Jonathan, et al. "Survival and Prognostic Factor Analysis of 146 Metastatic Neuroendocrine Tumors of the Mid-Gut." *Neuroendocrinology*, vol. 89, no. 4, 2009.
16. Hallet, Julie, et al. "Exploring the Rising Incidence of Neuroendocrine Tumors: A Population-Based Analysis of Epidemiology, Metastatic Presentation, and Outcomes." *Cancer*, vol. 121, no. 4, 2014.
17. Hauso, Oyvind, et al. "Neuroendocrine Tumor Epidemiology." *Cancer*, vol. 113, no. 10, 2008.

18. Ito, Tetsuhide, et al. “Epidemiological Trends of Pancreatic and Gastrointestinal Neuroendocrine Tumors in Japan: a Nationwide Survey Analysis.” *Journal of Gastroenterology*, vol. 50, no. 1, June 2014.
19. Tsikitis, Vassiliki L., et al. “Trends of Incidence and Survival of Gastrointestinal Neuroendocrine Tumors in the United States: A Seer Analysis.” *Journal of Cancer*, vol. 3, 2012.
20. Taal, B.g., and O. Visser. “Epidemiology of Neuroendocrine Tumours.” *Neuroendocrinology*, vol. 80, no. 1, 2004.