

NEUROENDOCRINE TUMORS: A REGISTRY OF 1000 PATIENTS

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SUMMARY

Neuroendocrine tumors (NET) can originate diffusely in most organs, with varying clinical presentations. The relative rarity of these tumors, previously referred to as carcinoids, encouraged several centers worldwide to study NET. Since 2003, a similar group was established in , the GETNE - Grupo de Estudo de Tumores Neuroendocrinos (Neuroendocrine Tumors Study Group) that included 32 centers, from all regions of Brasil. A patient database was initiated, collecting information about NET, regardless of the site of origin.

OBJECTIVES. The present study shows initial results of 1000 patients included. **METHODS:** Descriptive statistical analyses, as well as overall survival rates for different groups of NET patients registered by GETNE.

RESULTS. Most patients presented with thoracic NET (71.6%), while 20.2% had gastro-entero-pancreatic tumors. Median follow-up of all patients included was 33.7 months (range 1-141 months). At the time of the analysis, 29.3% of the patients were still alive (of these, 45.7% were alive with no evidence of disease).

CONCLUSION. This is the largest database of NET in, and further accrual of new patients, as well as individual study results are expected in the near future.

KEY WORDS: Carcinoid. Neuroendocrine tumor

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INTRODUCTION

Neuroendocrine tumors are neoplasms ubiquitously originating in most organs¹. The wide distribution and the varying clinical presentations, as well as the endocrine phenomena usually accompanying those tumors, hamper the efforts to establish sound and extensive experience in any single institution. Moreover, the relative rarity of neuroendocrine tumors clearly restricts the efforts of researchers to complete significant studies to define recommended approaches to all situations²⁻⁴. Since the early eighties, renewed interest in the study of neuroendocrine tumors emerged in different centers, with specialists teaming up to perform an ever-growing number of studies, mostly in the treatment of advanced and metastatic stages⁵. The identification of somatostatin receptors, present in over 85% of neuroendocrine tumors, and the introduction and commercialization of somatostatin analogs represented, not only a significant treatment option, but also a boost for clinical trials⁶⁻¹⁰. Recently, specialists interested in the study of neuroendocrine tumors created associations and cooperative groups to overcome the paucity of cases in most clinical practices. The most active representative of these groups is the ENETS, European Neuroendocrine Tumor Society.

In the early 2000, specialists practicing in Brazilian institutions initiated a group dedicated to discussing clinical situations, as well as experimental options, in patients with neuroendocrine tumors, the GETNE - Grupo de Estudo de Tumores Neuroendocrinos (Neuroendocrine Tumors Study Group). In 2003, GETNE decided to create a database of patients with neuroendocrine tumors to enable

local researchers to establish a working basis and access to clinical and pathological data from different medical centers around Brasil.

This study presents the preliminary results of the registry created by GETNE, with the future perspectives of the group.

METHODS

All specialists interested in joining GETNE were formally invited to participate in the database. All patients admitted since 1985, with the diagnosis (histology) of neuroendocrine tumor, even under different denominations like carcinoid, Merkel, medullary thyroid carcinoma, etc. were eligible to be included in the database. A simple data sheet was created and sent to all members of GETNE. The sheets were returned to a center in Sao Paulo, either by mail, fax, or via internet, and the data entered into a single database. Statistical analysis of the data accrued was performed on a monthly basis and results subsequently made available to GETNE.

Statistics: Descriptive analyses of the patients were included, as well as survival (Kaplan Meier) estimates were performed using SPSS 10.0 for Windows. Differences were considered significant for $p < 0.05$.

RESULTS

The first 1000 patients entered into the registry originated from 14 hospitals and cancer centers, as well as 18 individual clinics. The site of the primary tumor was not determined in 36 patients (Table 1). Symptoms related to the tumor were initially identified by 81% of the patient's complains in a wide range of periods, varying from one to over 16 months prior to admission in the referring center (median: 7

Table I - Site of the primary neuroendocrine tumor

Site	n	%
Thorax	716	71.6
GEP	202	20.2
Head and neck	15	1.5
Skin	9	0.9
Genitourinary tract	6	0.6
Adrenal	4	0.4
Biliary	3	0.3
Prostate	3	0.3
Esophagus	1	0.1
Breast	2	0.2
Kidney	1	0.1
Ovary	2	0.2
Unknown	36	3.6

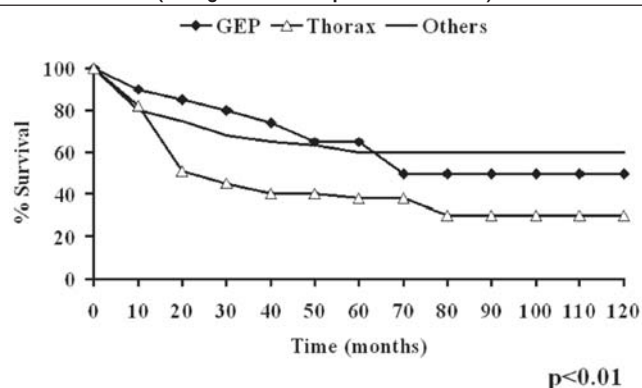
GEP: gastro-entero-pancreatic tumors

months). The diagnosis of neuroendocrine tumor relied solely on Hematoxylin and Eosin pathology report in the vast majority of cases (79.3%). Only 207 patients had further immunohistochemical staining performed in order to confirm the final diagnosis. Proliferation index (Ki-67) was reported in 17 cases (1.7%). Most patients presented with locoregional disease on admission (46.2%), with 108 cases missing the initial stage information in their charts. Neuroendocrine tumors with distant metastases on admission were diagnosed in 430 patients. Along with the routine imaging (X-rays, ultrasound and CT scans, as well as MRI scans), octreoscans were performed on 114 patients (11.4%), and MIBG-meta-iodo-benzyl-guanidine scans on 37 patients (3.7%). Arteriography was performed on two patients. Whole body scanning with FDG-PET was registered in 11 patients (1.1%). Laboratory determination of neuroendocrine tumor markers (blood and/or urine samples) was performed in 109 patients (10.9%).

Treatment modalities of the patients entered into the registry included surgery (35.1%), chemotherapy (59.9%), radiotherapy (20.4%), somatostatin analogs (4.2%), radioactive octreotide therapy (1.9%), radioactive MIBG therapy (0.3%), interferon (1.9%), arterial embolization (0.5%) and chemoembolization (0.8%). Median follow-up of all patients included was 33.7 months (range 1-141 months). At the time of the present analysis, 29.3% of the patients were still alive (of these, 45.7% were alive with no evidence of disease). Fifty-two patients were lost of follow up from their referring center. Overall survival curves are shown in Figure 1.

DISCUSSION

Neuroendocrine tumors (NETs) are relatively rare, with less than 10 new cases estimated to be diagnosed annually per one million persons. The infrequent occurrence of these tumors makes a large experience of individual medical institutions, let alone physicians, very unlikely. A group of Brazilian oncologists joined efforts to establish a comprehensive database (Grupo de Estudo de Tumores NeuroEndocrinos-GETNE), including patients with the diagnosis of neuroendocrine tumors, irrespective to their site of origin. Similarly to

Figure 1 - Overall survival curves of patients included in GETNE, according to the site of primary tumor. (GEP: gastro-entero-pancreatic tumors)

other entities around the world, like ENETS, GETNE was started in meeting discussions among specialists interested in the study and the management of NETs. Since its establishment, the database included over 1000 patients, originated from centers throughout Brasil. Basic information from analyses of the database shows that the most frequently registered NETs were thoracic in origin, followed by gastro-entero-pancreatic tumor, and head and neck. This is not consistent with the known epidemiology of NETs, as shown by the classic studies published by Modlin and others¹¹. We believe that the results of the present data reflect solely the bias of the first referring centers that registered the patients, with an overwhelming majority from reference cancer centers for thoracic tumors. We expect that further inclusion of patients from other centers and Brazilian regions would correct this distortion, and offer a better sample of the current distribution of NETs in Brasil. The present database has no intention to replace the official National Cancer Institute's registry (Inca, Ministério da Saúde), and will always represent the patient population treated at the participating centers. Survival rates were significantly different, depending on the site of origin (Figure 1), consistent with results published in previous studies^{1,2,11,12}.

The ongoing accrual of patients and inclusion into this database represents a pioneering effort to provide the interested scientific community in Brasil with basic information on a comprehensive number of patients with different NETs. Presently, GETNE is starting several investigative projects including specialties like pathology, medical and surgical oncology, and nuclear medicine. We expect more detailed results from these studies in the near future.

Conflict of interest: none

RESUMO

TUMORES NEUROENDÓCRINOS: REGISTRO DE 1000 PACIENTES

Os tumores neuroendócrinos (TNE) podem se originar da maioria dos órgãos com apresentação clínica variável. A relativa raridade destes tumores, previamente classificados como carcinóides, levou vários centros

no mundo a realizar estudos específicos dos TNE. A partir de 2003, um grupo similar foi criado no , GETNE- Grupo de Estudo de Tumores Neuroendócrinos, que incluiu 32 centros médicos de várias regiões do Brasil. Um arquivo de pacientes foi criado, registrando informações individuais sobre TNE, independente do órgão de origem. OBJETIVOS: O presente estudo apresenta os resultados dos primeiros 1000 pacientes incluídos.

MÉTODOS. Análise estatística descritiva, assim como análises de sobrevida global dos pacientes registrados no GETNE.

RESULTADOS. A maioria dos pacientes foi admitida com TNE torácicos (71,6%), enquanto 20,2% tiveram TNE gastro-entero-pâncreáticos. O seguimento mediano foi de 33,7 meses (variando entre 1-141 meses). Ao término desta análise, 29,3% dos pacientes ainda estavam vivos (destes, 45,7% vivos sem evidência de doença).

CONCLUSÃO. Este representa o maior arquivo de TNE no , e a inclusão de novos pacientes, assim como estudos específicos, são esperados no futuro próximo. [Rev Assoc Med Bras 2008; 54(4): 305-7]

UNITERMOS: Carcinóide. Tumores neuroendócrinos.

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