RESEARCH ARTICLE

Digestive Neuroendocrine Tumor Distribution and Characteristics According to the 2010 WHO Classification: a Single Institution Experience in Lebanon

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Abstract

Background: Gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NEN) are relatively rare tumors, not equally distributed in gastro-intestinal system. In 2010, a revised version of the WHO classification of GEP-NENs was published. This study reports for the first time the distribution and characteristics of GEP-NEN in a Lebanese population. Materials and Methods: This descriptive retrospective study concerns all the digestive neuroendocrine tumors with their characteristics diagnosed in Hôtel Dieu de France in Beirut, Lebanon from 2001 to 2012, all the pathology reports being reanalyzed according to the latest WHO 2010 classification. The characteristics and features of GEP-NEN analyzed in this study were age, gender, grade and site. Results: A total of 89 GEP-NENs were diagnosed, representing 28.2% of all neuroendocrine tumors. The mean age of GEP-NEN patients was 58.7 years and the M/F sex ratio was 1.2. The primary localization was as follows: 21.3%(19) pancreatic, 18% (16) gastric, 15.7% (14) duodenal, 11.2% (10) appendix, 10.1% (9) intestinal, 10.1% (9) colorectal (7.9% colonic and 2.2% rectal), 5.6% (4) hepatic, 2.2% (2) ampulla, 1.1% (1) esophageal and 7.9%(5) NOS digestive (metastatic with unknown primary). Of the 89 patients with GEP-NEN, 56.2% (50) were diagnosed as grade I, 11.2% (10) as grade II, 20.2% (18) as grade III and 12.4% (11) were considered as mixed adeno-neuroendocrine carcinomas (MANEC). Conclusions: This study, one of the rare examples based on the 2010 WHO classification of neuroendocrine tumors in the literature, indicates that in the Lebanese population, all duodenal and appendicular tumors are G1 and the majority of MANEC tumors are gastric and pancreatic tumors. Moreover, more duodenal tumors and fewer rectal tumors were encountered in our study compared to European reports.

Keywords: WHO 2010 - GEP-NEN - digestive neuroendocrine tumors - Lebanon

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Introduction

Gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs) derive from gastrointestinal stem cells that are able to differentiate into neuroendocrine cells. These tumors can occur anywhere in the GEP neuroendocrine cell system. However, they are not equally distributed (Klöppel et al , 2007). Tumors are thus more frequently observed at certain sites such as gastric fundus–corpus, proximal duodenum, Vater's papilla, terminal ileum, tip of the appendix, lower rectum and pancreas.

In 2010, a revised version of the WHO classification of GEP-NENs was published (Rindi et al , 2010 , Scoazec et al 2010 and Klöppel et al 2011). GEP-NENs are divided into pure and non-pure tumors. The pure NENs of the gastrointestinal tract and pancreas are stratified into two groups: the well-differentiated NE tumors (NETs) and the poorly differentiated NE carcinomas (NECs).

The NETs are then separated into G1 (equivalent to carcinoids) or G2 NETs based on their proliferative activity. The mitotic count is evaluated in 50 high power fields (HPFs) of 2 mm^2 each, and counted in 10 HPFs. G1 tumors are thus defined as well differentiated neuroendocrine tumors having a mitotic count less than 2 and a Ki67 index ≤2%. G2 tumors are defined as well differentiated neuroendocrine tumors as well, but having a mitotic count between 2 and 20 and a proliferation index Ki67 between 3 and 20%.

The NE carcinomas are poorly differentiated tumors, called G3. They are subdivided into small cell and large cell neoplasms.

The neoplasms that show in addition to neuroendocrine cells (exceeding at least 30% of all tumour cells) non-endocrine components (usually glandular differentiation)

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are distinguished and called mixed adenoneuroendocrine carcinomas (MANECs).

There has been no previous publication regarding GEP-NENs in Lebanon. We hereby report for the first time their distribution.

Materials and Methods

This is a descriptive retrospective study reporting all the digestive neuroendocrine tumors with their characteristics diagnosed in Hotel Dieu de France in Beirut, Lebanon from 2001 to 2012. The data was collected from the pathology department computerized database. All NETs were first selected, duplicated cases were detected and then NETs were distributed according to their primary site (pulmonary, digestive and others). All the pathology reports of selected patients were revised and specimens reanalyzed according to the latest WHO 2010 classification of NET tumors.

The characteristics and features of GEP-NEN analyzed in this study were age, gender, grade and site of the neuroendocrine tumors. All the results were analyzed using the SPSS version 20.

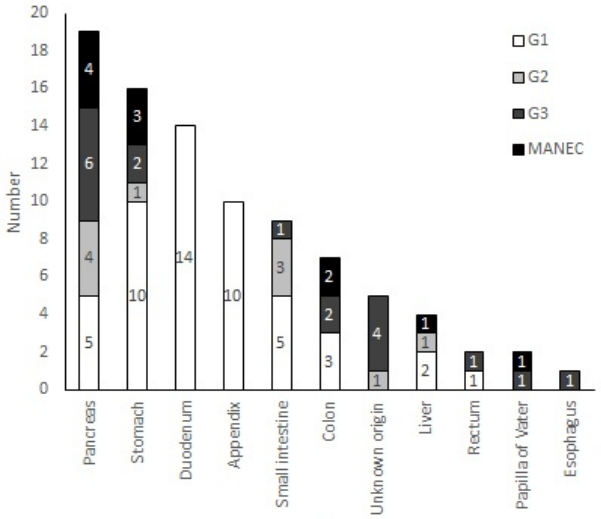

Figure 1. Distribution of GEP-NEN According to the Site and the Grade

Table 1. Numbers, Proportions, Mean Agea and Sex Ratios of Different Grades of GEP-NEN

	Number	Proportion	Mean Age	M/F Sex Ratio
G1	50	56.20%	57.24	1.2
G2	10	11.20%	56.4	0.4
G3	18	20.20%	60.89	2.6
MANEC	11	12.40%	64.18	1.2
Total	89	100%	58.74	1.2

Results

Among the 316 NET tumors diagnosed in Hotel Dieu de France from 2001 to 2012 (including the small cell and large cell neuroendocrine tumors of the lung), 89 were GEP- representing 28.2% of all NET. The mean age of GEP-NEN is 58.7 years and the M/F sex ratio is 1.2. The mean age in male patients was of 60.3 years, compared to 56.8 years in female patients.

The GEP-NENs were distributed according to the primary localization as follow: 21.3%(19) pancreatic NET, 18% (16) gastric NET, 15.7% (14) duodenal NET, 11.2% (10) appendix NET, 10.1% (9) intestinal NET, 10.1% (9) colorectal NET (7.9% colic and 2.2% rectal), 5.6% (4) hepatic NET, 2.2% (2) ampulla NET, 1.1% (1) esophageal NET and 7.9% (5) NOS digestive NET (cases diagnosed on a metastatic site, expressing CDX2 by IHC, without any primary detected) .

From these 89 patients with GEP-NEN, 56.2% (50) were diagnosed at grade I, 11.2% (10) at grade II, 20.2% (18) at grade III and 12.4% (11) were considered as MANEC (Figure 1). The mean age of patients according to the grade were respectively 57.2 years in grade I, 56.4 years in grade II, 60.9 years in grade III and 64.2 years in MANEC. The M/F sex ration of these patients according to the grade is respectively 1.2 in grade I, 0.4 in grade II, 2.6 in grade III and 1.2 in MANEC (Table 1).

When combining the two variables (grade and location), we find that all duodenal and appendicular NETs are grading I, while the wide majority of MANEC are pancreatic, gastric and colic NET.

Discussion

All the neuroendocrine tumors and carcinomas were included in our study and the methodology was not limited to carcinoid tumors (G1 and G2), as described in some other studies (Helland et al., 2006 and Maggard et al., 2004). When comparing our results to those of other studies led in different European and American countries,

Table 2. Comparison of the Distribution of GEP-NEN According to their Primary Site in Different Countries

	Lebanon	Austria	Germany	Spain	France	Poland	China
Years	2001-2012	2004-2005	1999-2010	2000-2009	2001-2002	2002-2011	2001-2013
Reference	Kourie et al. 2015	Niederle et al. 2010	Begum et al. 2010	Galvan et al. 2014	Lombard-Bohas . 2009	Lewkowicz et al . 2015	Jiao et al. 2015
Number of patients	89	285	2009	110	668	122	154
Pancreas	24.7%	11.9%	41.8%	20.0%	37.4%	18.9%	40.90%
Stomach	20.8%	23.5%	7.9%	16.4%	5.9%	17.2%	22.10%
Duodenum	18.2%	5.8%	5.8%	25.5%	51.1%	20.5%	4.50%
Small intestine	11.7%	15.9%	31.6%				
Colon	9.1%	7.2%	8.4%	20.9%		9.0%	27.90%
Rectum	2.6%	14.4%			2.1%	18.9%	
Appendix	13.0%	21.3%	4.5%	17.3%	3.5%	15.5%	

many differences in population characteristics going from sex ration, age to the site of the digestive primary, were noted.

The mean age and the M/F sex ratio of GEP-NENs are similar to those reported in the literature: the mean age is around 56 in France (Lombart et al., 2007), China (Jiao et al., 2015) Germany (Begum et al., 2014) and Spain (Galvan et al., 2013); the sex ratio lies between 0.85 and 1.17 in the same studies. The mean ages of male and female patients are slightly lower than those reported in the Austrian study (60.3 versus 63 years in male patients and 56.8 versus 59 years in female patients) (Niederle et al., 2013).

The repartition of the most frequently reported primary localization within the digestive tract are summarized and compared to international data in Table 2. The high proportion of pancreatic tumors reported in our study are comparable to those in Germany (Begum et al., 2014), Spain (Begum et al., 2014) and France (Lombart et al., 2007) (ranging from 20.0 to 41.8%), in contrast to Austria, where it does not exceed the 11.9% (Niederle et al., 2013). Gastric tumors represent more than 15% of all digestive GEP-NEN in our study; similar rates have been observed in Austria (Niederle et al., 2013) and Spain (Galvan et al., 2013). The rates of gastric tumors in other countries ranged between 5.9 and 8.5%. The proportions of neuroendocrine tumors in the duodenum, small intestine, colon and rectum vary largely between different listed countries; their repartition was unique and specific in each country. Regarding the appendix neuroendocrine tumors, low rates were reported in France (Lombart et al., 2007) and Germany (Begum et al., 2014) (respectively 3.5 and 4.5%) and higher rates in Spain (Galvan et al., 2013) and Austria (Niederle et al., 2013) (ranging from 17.3 to 21.3%). Our rate ranged between those previously mentioned (13.0%). On a side note, a particularly high rate of rectum neuroendocrine tumors has been reported on numerous occasions in some Asian countries (Jiao et al., 2015).

Concerning the grading of tumours, most primary tumours of the stomach, duodenum, appendix, small intestine, liver and rectum were well differentiated (G1 or G2). Tumours originating from the pancreas, the papilla of Vater and the colon were mostly poorly differentiated or associated to an adenocarcinoma (G3 or MANEC). Those results are concordant with what is reported in the literature.

In conclusion, Our study is one of the rare based on WHO classification of 2010 for neuroendocrine tumors. In our population, all duodenal and appendicular tumors are G1. The majority of MANEC tumors are gastric and pancreatic tumors. More duodenal tumors and less rectal tumors are reported in our study compared to European studies.

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