

# A STUDY OF THE FREQUENCY AND LOCALIZATION OF THE GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS DIAGNOSED AND OPERATED AT THE UNIVERSITY HOSPITAL - PLEVEN IN 2014

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## ABSTRACT

**Objective:** Over 90% of neuroendocrine tumors (NETs) in Bulgaria were reported to arise in the gastrointestinal tract. Our objective was to study the incidence and localization of the gastroenteropancreatic NETs, diagnosed for one year.

**Methods:** The present retrospective study explores the incidence and localization of the gastroenteropancreatic NETs, diagnosed and operated for one year period (during 2014) in UMHAT “Dr. Georgi Stranski”, Pleven.

**Results:** Seven cases of gastroenteropancreatic NETs were diagnosed and treated for the studied period. Most common primary sites were: pancreas in 4 (57.14 %) cases and 2 in colon (28.57 %) cases. According to the morphological criteria, 2 (28.57 %) were well differentiated NETs, 3 (42.86 %) were moderately differentiated, and 2 (28.57 %) were poorly differentiated NETs. One of them was mixed adenoneuroendocrine carcinoma. All cases demonstrated immunoeexpression of Chromogranin A and Synaptophysin in addition to the distinct neuroendocrine morphology. Distant site metastases were observed in 5 (71.43 %) cases.

**Conclusion:** According to our results, most of the gastroenteropancreatic NETs were well and moderately differentiated and located in pancreas. A considerable number of patients had distant metastasis at the time of diagnosis. The expression of Chromogranin A and Synaptophysin supported the morphological diagnosis of gastroenteropancreatic NET.

**Keywords:** *gastroenteropancreatic NETs, incidence, localization*

## INTRODUCTION

The frequency of the neuroendocrine tumors (NET) is increasing by 5.8 % per year<sup>1</sup>, mostly due to the improved diagnostic approaches. They are a heterogenic group of tumors that can develop in every organ of the human body, but are predominant in the pancreas and the gastrointestinal tract.<sup>1</sup> Gastroenteropancreatic tumors can be found most often in the small intestines (30.8), rectum (26.3%), large intestine (17.6%), pancreas (12.1%) and appendix (5.7%).<sup>1</sup>

Primary epidemiological information about the frequency of the neuroendocrine tumors in Bulgaria was collected in 2013. The initial information includes 127 patients with NET from the regions of Sofia, Varna and Pleven. 98% of the tumors are with a localization in the gastrointestinal tract. The small intestines, rectum and appendix are most affected, while the gut, stomach and pancreas are less affected.

There are no specific symptoms with this type of tumors.<sup>2,3,4</sup> NET are usually

diagnosed late because of their unpredictable biological behavior. 50% of the cases are with metastases at the moment of diagnosing. In 27% of the cases the metastases are distant, while in 23% the metastases are regional and because of that the possibilities for antitumor treatment are limited.<sup>3,4,5</sup> Several universal plasma tumor markers are used for diagnosing NET with different primary localization. The isolated increase of any of them is insufficient for the diagnosing of NET without histological verification. Gastroenteropancreatic tumors show slow biological progress, but are with notable malignant potential. The bigger part of them are not active functionally. The immunohistochemical characteristic of NET includes expression of 3 basic markers: neuron specific enolase-cytosolic marker, synaptophysin - transmembrane glycoprotein, located in the presynaptic vesicles of the neurons and chromogranins-soluble acid glycoproteins, located in the matrix of the neurosecretory granules. Chromogranin A is a universal marker for the neuroendocrine tissue and it's a precursor of pancreatostatin. Histological diagnosing requires obligatory immunohistochemical investigation which must include the basic markers: chromogranin A and synaptophysin. Immunohistochemical investigation for Ki-67-nuclear cell marker for determination of the proliferative potential of the tumors is recommended as standard.

The purpose of our presentation is the study of the frequency and localization of the gastroenteropancreatic tumors, diagnosed and operated on at University Hospital- Pleven for the period of one year (2014).

## MATERIALS AND METHODS

This is a retrospective study covering a period of one year. The patients included were operated on at the surgical clinics of the University Hospital - Pleven.

The patients in this study were operated on because of a tumor process of the colon,

rectum and pancreas. Patients on whom an appendectomy was performed in the surgical clinics of the University Hospital - Pleven during 2014 are included as well. All patients underwent immunohistochemical investigation of the tumor material stored in a paraffin block at the Clinic of Pathoanatomy - University Hospital - Pleven.

The following methods are used in this study: 1.) Clinical; 2.) Clinicopathologic; 3.) Immunohistochemical.

1. Clinical Methods – information about the sex and age of the patients at the date of their operation is used.

2. Clinicopathologic Methods – the information about the histological type of the tumor, TNM- classification is used.

3. Immunohistochemical Investigation. The criteria of the World Health Organization and the European Association for Neuroendocrine Tumors (ENETS) are used in this study of pathomorphological assessment of the gastroenteropancreatic tumors. They include immunohistochemical verification of the neuroendocrine origin of the tumor (Positive chromogranin A and/or Synaptophysin), staging by the requirements of the 7th edition of the pTNM classification, mitotic index and/or Ki-67 proliferative index.

## RESULTS

7 cases of patients with gastroenteropancreatic tumors were diagnosed and operated on at the University Hospital – Pleven in 2014. The tumors were most frequently located in the pancreas - 4 patients (57.14%). In 2 patients (28.57 %) the rectum was affected and in 1 patient it was a case of adenoneuroendocrine tumor, the so-called MANEC. Female to male ratio is 7/6. In 5 patients distant metastases were found.

## DISCUSSION

*Table 1. Distribution of the gastroenteropancreatic NET for 2014 by age, sex, localization and histological type.*

<b>№</b>	<b>Age</b>	<b>Sex</b>	<b>localization</b>	<b>Diagnosis</b>	<b>Grade of differentiation</b>
1.	64	Female	Large intestine T4NxM1	Neuroendocrine neoplasm	G2
2.	44	Female	Pancreas	Neuroendocrine tumor	G2
3.	69	Female	Rectum	MANEC	G3
4.	56	Female	Pancreas	Neuroendocrine tumor	G2
5.	40	Female	Rectum	Neuroendocrine carcinoid	G1
6.	62	Male	Pancreas	Neuroendocrine carcinoma	G3
7.	60	Female	Pancreas T3N1M0	Neuroendocrine carcinoma	G1

The frequency of the gastroenteropancreatic neuroendocrine tumors increases every year according to recent European investigations.<sup>1</sup> The knowledge about these tumors is still insufficient and they are diagnosed late. The prognosis for the gastroenteropancreatic NETs depends on several clinicopathologic indices and on the histological type of the tumor:

- Grade of differentiation,
- Size of the tumor,
- Metastases in the regional lymphatic nodules,
- Stage of the disease.

The criteria mentioned above are not always sufficient for a deep and objective assessment of the NETs. More precise and deeper investigation of the immunohistochemical indices is needed for the clarification of the biological behavior of these tumors. Effective predictive markers showing the susceptibility to concrete type of antitumor treatment must be found and effective diagnostic markers that help the diagnosis of the different histological types of NET are needed as well.

Our investigation shows increase in the frequency of gastroenteropancreatic NETs in Bulgaria. Our future task will be to discover which immunohistochemical indices could be used as prognostic and predictive markers for

the prognosis and the therapeutic approach to these tumors.

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