

## NEUROENDOCRINE TUMORS (NET) OF THE GASTROINTESTINAL SYSTEM: DIAGNOSIS AND THERAPY

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Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a rare and heterogeneous group of tumors arising from the cells of diffuse endocrine system (DES) scattered through the mucosa of the gastrointestinal tract and pancreas. Tumors were historically termed carcinoid-«cancer-like» due to better prognosis than adenocarcinoma. Yearly incidence of GEP-NETs is estimated to be 1-2 of 100.000 population, but according to newer population registries data and autopsy reports it has increased by 5-folds, much more than incidence of other gastrointestinal malignancies. A special feature of these neoplasms is amine precursor uptake and decarboxylation, leading to production of hormones and bioactive amines (tachykinines, bradykinines, etc.), and therefore a potential for causing specific hypersecretory syndromes (such as WDHA, Zollinger-Ellison, carcinoid, hypoglycemic, glucagonoma, somatostatinoma etc.). Another characteristic is a potential to arise accompanied by other endocrine gland tumors, associated into syndromes of multiple endocrine neoplasia type I (MEN I), neurofibromatosis type I (NF I), and von Hippel Lindau disease. According to World Health Organization (WHO), GEP-NETs are categorized into well-defined tumors (benign or low grade malignant), well-defined neuroendocrine carcinoma and poorly differentiated neuroendocrine carcinoma. The classification is based on proliferative activity measured by Ki67 index, number of mitoses, local invasiveness or metastatic potential and according to the secretory status of tumors. Newer classification combines WHO and TNM classification, and categorizes GEP-NETs into G1 and G2- well-differentiated; or G3-low differentiated

tumors where T3 and T4 (>4cm and local invasions) defines local and N1 (lymphnodes) and M1 (liver) metastases. Due to nonspecific symptoms mimicking many different diseases, GEP-NETs are unfortunately often diagnosed late in the course of disease (with on average 5-7 years delay). Most GEP-NETs are actually nonfunctional, i.e. not associated with recognizable clinical syndromes. Prominent symptoms rising suspicion of GEP-NETs are diarrhea and flushing, but they are most common when tumors metastasize. Diagnosis of GEP-NETs is based on clinical syndromes, specific tumor markers measured in serum or urine of patients, and confirmed by histopathology reports and imaging techniques. Chromogranin A (CgA) represents a general neuroendocrine marker, important in not only diagnostic procedures but also in follow-up of patients. In patients with carcinoid (serotonin-producing GEP-NETs), important marker is serum serotonin level, or more often measured serotonin metabolite 5-hydroxyindolacetic acid, measured in 24-hour urine output. For the histopathological confirmation of GEP-NETs positive immunohistochemical staining for CgA, synaptophysin, neuron-specific enolase (NSE) are needed. Informative histopathological report must also include Ki67 index and number of mitoses in tumor tissue. A gold standard in imaging procedures is octreoscan, but newer radionuclide imaging procedures such as PET combined with tracers such as  $^{11}\text{C}$ -5-HT or  $^{68}\text{Ga}$ -DOTATOC will in future develop as most effective methods of imaging detection. Endoscopic procedures, especially endoscopic ultrasound are important due to possibility of tissue sampling and cytological/hystological tumor confir-

mation. GEP-NETs are potentially curable when surgery is performed in early staged tumors. Surgical treatment is also important for abrogation of symptoms, even in cases of advanced GEP-NETs. In cases of functionally active tumors, causing specific, previously mentioned syndromes, biotherapy in form of somatostatin analogues is used but effects produced through receptor subtype 2 are thought also to cause tumor apoptosis and proliferation inhibition. Somatostatin ( $^{111}\text{In}$ -DTPA-octreotide,  $^{90}\text{Y}$ -DOTA-octreotide and  $^{177}\text{Lu}$ -DOTA-octreotide) is also used as a basis of

receptor targeted radionuclide therapy. Chemotherapy for treatment of GEP-NETs has a limited effect, and is used in advanced tumors, with somewhat better response seen in cases of pancreatic neuroendocrine tumors (up to 60%). Currently many new agents, especially that targeting tumor cell proliferation are under investigation for treatment of GEP-NETs. Promising results come from studies investigating mTOR inhibitors, tyrosine kinase inhibitors for different growth factors, especially VEGF.