

Management of gastroenteropancreatic neuroendocrine neoplasms: an ongoing challenge

Tomasz Bednarczuk

Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are rare, constituting only 1% to 2% of all neoplasms. They originate from neuroendocrine cells: up to 65% in the gastrointestinal tract, about 25% in the bronchopulmonary system, and the remaining 10% at other sites. It is a very heterogeneous group of neoplasms with a wide range of aggressiveness. Moreover, the natural course of GEP-NEN is difficult to predict. A correct histological diagnosis is crucial for the management of NEN; tumors categorized according to the Ki67 index require different treatment strategies.^{1,2} Well-differentiated NENs are graded as G1 (Ki-67 $\leq 2\%$) and G2 (Ki67, 3%–20%). The poorly differentiated neoplasms are called neuroendocrine carcinomas (NEC) and are graded as G3 (Ki67 $> 20\%$).

Despite great progress, there is still a limited number of prospective randomized studies that might provide the grounds for strong evidence-based recommendations. Moreover, diagnostic procedures and treatment options differ significantly in many countries because of their different availability.^{3–5} Therefore, there is a great need for epidemiological studies that might evaluate the outcome of GEP-NEN and define potential predictive factors.

According to the Surveillance Epidemiology and End Results (SEER) study, based on United States epidemiological data, covering from 10% to 14% of the American population, the number of patients with NEN has been increasing annually from 1969 to 2004. The overall incidence of GEP-NEN increased 2- to 3-fold during this 35-year period. Recent epidemiological data from England, Norway, and Germany are in line with a recent report from the SEER registry and showed an increase in the detection of GEP-NEN.^{6–12} The observed changes may in part reflect the increased number of asymptomatic GEP-NEN identified incidentally thanks to increased availability of modern endoscopic and radiological imaging techniques.¹⁰

GEP-NEN occur in approximately 1.3 to 3.8 per 100 000 population. The most frequent primary sites (with variable numbers in different studies) are the small intestine, pancreas, appendix, rectum, stomach, and colon.

The study of Lewkowicz et al.¹³ is particularly interesting because it is the first report of clinical and histopathological features and prognostic factors of GEP-NEN patients in a single center in Poland. The most common primary origin of GEP-NEN in the evaluated population were the small intestine (20%) and pancreas (19%). The overall 5-year survival was 85%, and it was associated with the following: 1) primary tumor location (poorer prognosis was noted for the small intestine, pancreas, and colon; however, the differences were not significant [$P = 0.06$]—similarly to the German registry)⁹; 2) higher grade (poorer prognosis was noted in NEN G2; univariate analysis, $P = 0.003$); and 3) higher stage and metastases at diagnosis (univariate analysis, $P < 0.001$). Importantly, distant metastases at diagnosis were found in almost one-fourth of the cases, most often in pancreatic and small intestinal NENs. What is more, the results of this study emphasize the need for more detailed cancer screening in patients with GEP-NEN. In this material, 16% of the patients had coexisting neoplasms. In literature, the coincidence of another tumor ranges from 10% to 32%.

The study presented by Lewkowicz et al.¹³ is not without limitations. Due to a small number of NEC G3 ($n = 5$), the results in this subgroup have to be interpreted with caution. Moreover, there was a relatively small group of patients with hormonally active GEP-NENs ($n = 11/121$), especially small intestine NEN with carcinoid syndrome (no patients). The comparison between different databases is also difficult because their classification and nomenclature have significantly changed in recent years.

Correspondence to:

Prof. Tomasz Bednarczuk, MD, PhD, Katedra i Klinika Chorób Wewnętrznych i Endokrynologii, Warszawski Uniwersytet Medyczny, ul. Banacha 1a, 02-097 Warszawa, Poland, tel.: +48 22 599 29 75, fax: +48 22 599 19 75, e-mail: tomasz.bednarczuk@wum.edu.pl

Received: May 17, 2015.

Revision accepted: May 18, 2015.

Conflict of interests: none declared.

Pol Arch Med Wewn. 2015;

125 (5): 319–320

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In conclusion, the study by Lewkowicz et al.¹³ significantly improves our knowledge about the epidemiology of GEP-NENs in Poland. The identification of factors influencing survival of patients with GEP-NENs is crucial for an appropriate treatment plan. It is also important to avoid overtreatment in patients with good prognosis and to secure more intensive treatment modalities in patients with poorer prognosis. Although most NEN G1 (86%) were diagnosed as localized disease, most NEN G2 (79%) were diagnosed as disseminated disease. This underscores the need for early GEP-NEN detection, which may significantly improve patients' outcomes.

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