



Epidemiology of gastroenteropancreatic neuroendocrine neoplasms in Krakow and Krakow district in 2007–2011

Epidemiologia nowotworów neuroendokrynych układu pokarmowego w Krakowie i powiecie krakowskim w latach 2007–2011

Małgorzata Trofimiuk-Müldner^{1,2}, Ewelina Lewkowicz², Katarzyna Wysocka³, Dorota Pach^{1,2}, Agnieszka Kiełtyka⁴, Agnieszka Stefańska², Anna Sowa-Staszczak^{1,2}, Romana Tomaszewska³, Alicja Hubalewska-Dydejczyk^{1,2}

¹Chair and Department of Endocrinology, Jagiellonian University, Medical College, Krakow, Poland

²Department of Endocrinology, University Hospital in Krakow, Krakow, Poland

³Chair of Pathomorphology, Jagiellonian University, Medical College, Krakow, Poland

⁴Chair of Epidemiology and Preventive Medicine, Jagiellonian University, Medical College, Krakow, Poland

Abstract

Introduction: Gastroenteropancreatic neuroendocrine neoplasms (GEPNEN) are rare and heterogeneous tumours with variable biology. The aim of this study was to evaluate the epidemiology of GEPNEN in the population of Krakow and Krakow district in 2007–2011.

Material and methods: The Database of the Chair and Department of Endocrinology, Jagiellonian University Medical College, comprising the data on NEN cases collected from the Endocrinology Department, University Hospital in Krakow and from independent sources: surgery, pathology, and endocrinology departments located in the Krakow area, was searched for cases of GEPNEN patients living in Krakow and Krakow district, diagnosed between 2007 and 2011. Eighty-eight such patients (39 males, 49 females, median age at diagnosis 59 ± 17 years) were identified and characterised.

Results: The mean follow-up time was 2.67 ± 1.6 years. The most frequent primary location of GEPNEN was small intestine (20%), followed by the appendix (18%), stomach (16%), pancreas (16%), rectum (15%), and colon (15%). NENG1 predominated (64%) in the analysed group. Most well-differentiated GEPNEN (63%) were diagnosed at stage I; however, 18% of them were diagnosed at stage IV. Metastases at diagnosis were found in 31% of patients. The GEPNEN incidence rate in 2007–2011 was 2.1/100000 inhabitants/year, without significant increase during the studied period.

Conclusions: GEPNEN incidence and epidemiology in the population of Krakow and Krakow district is similar to the incidence observed in most European countries. Registers are important tools to evaluate GEPNEN epidemiology. (*Endokrynol Pol* 2017; 68 (1): 42–46)

Key words: gastroenteropancreatic neuroendocrine neoplasms; incidence; epidemiology

Streszczenie

Wstęp: Nowotwory neuroendokryne układu pokarmowego (GEPNEN) stanowią rzadką i heterogenną grupę guzów o zróżnicowanej biologii. Celem pracy była ocena epidemiologii GEPNEN w populacji Krakowa i powiatu krakowskiego.

Materiał i metody: W Rejestrze Katedry i Kliniki Endokrynologii, Collegium Medicum Uniwersytetu Jagiellońskiego, zawierającym dane pacjentów z NEN z Oddziału Klinicznego Endokrynologii, Szpitala Uniwersyteckiego w Krakowie oraz z niezależnych źródeł: oddziałów chirurgicznych, pracowni patomorfologicznych i oddziałów o profilu endokrynologicznym z terenu Krakowa, wyszukano chorych z GEPNEN zamieszkujących w Krakowie lub powiecie krakowskim, zdiagnozowanych w latach 2007–2011. Znalezione i scharakteryzowano 88 takich przypadków (39 mężczyzn, 49 kobiet, średni wiek w chwili rozpoznania 59 ± 17 lat).

Wyniki: Średni czas obserwacji wynosił 2.67 ± 1.6 lat. Najczęstszą lokalizacją ogniska pierwotnego GEPNEN było jelito cienkie (20%), następnie wyrostek robaczkowy (18%), żołądek (16%), trzustka (16%), odbytnica (15%) i jelito grube (15%). W badanej grupie przeważały NENG1 (64%). Większość wysoko zróżnicowanych GEPNEN (63%) rozpoznano w stopniu I klinicznego zaawansowania, jednakże 18% z nich w stopniu IV. U 31% pacjentów w momencie rozpoznania stwierdzono przerzuty. Współczynnik zapadalności na GEPNEN w latach 2007–2011 wynosił 2,1/100000 osób/rok, bez istotnego wzrostu w badanym okresie.

Wnioski: Współczynniki zapadalności i epidemiologia GEPNEN w populacji Krakowa i powiatu krakowskiego były podobne jak w większości krajów europejskich. Rejestry stanowią istotne narzędzie w ocenie epidemiologii GEPNEN. (*Endokrynol Pol* 2017; 68 (1): 42–46)

Słowa kluczowe: nowotwory neuroendokryne układu pokarmowego; zapadalność; epidemiologia

Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEPNEN) are rare, but increasing in incidence, poorly

understood, heterogeneous neoplasms with different malignant potential. They derive from the diffuse neuroendocrine system [1]. Although significant progress in the diagnosis and treatment of GEPNEN has been achieved

✉ Ewelina Lewkowicz M.D., Department of Endocrinology, University Hospital in Krakow, Kopernika St. 17, 31–501 Kraków, Poland, phone: +48 12 424 75 00, fax: +48 12 424 73 99, e-mail: baczynskae@yahoo.com

in recent years, they still pose a dilemma for physicians of all specialties [2]. Early diagnosis, essential for radical therapy, is usually difficult due to non-specific presentation of most GEPNEN [3]. Another problem is that patient stratification into prognostic risk groups and identification of subjects requiring frequent monitoring and more aggressive treatment. Furthermore, the nomenclature and classifications of GEPNEN are continually changing. The WHO classification, which is based on grading, has not been adopted worldwide. Currently, there are two parallel TNM staging classifications, by the AJCC/UICC and the ENETS. Despite the same terminology they differ substantially and should be used carefully [4].

The inconsistency of nomenclature and classification constitutes a severe limitation in assessing the precise epidemiology of GEPNEN, recording the data, and comparing them. Another difficulty is that many registries dedicated to NEN patients are not population based, which makes calculation of incidence rates of these neoplasms impossible [4].

The aim of this study was to evaluate the epidemiology of GEPNEN in Krakow and Krakow district in 2007–2011.

Material and methods

The analysis included the data from the Neuroendocrine Neoplasms Database of the Chair and Department of Endocrinology, JUMC, based on medical records from the Endocrinology Department, University Hospital in Krakow, and from independent sources: surgical wards, pathomorphology units, and other wards of the endocrine profile in Krakow. At the moment the register comprises 584 subjects. For further analysis, patients with histologically confirmed GEPNEN diagnosed from 01.01.2007 to 31.12.2011 living in Krakow and Krakow district were identified.

Age at diagnosis, gender, place of residence (Krakow vs. Krakow district), primary site of GEPNEN, grading according to the WHO 2010 classification, staging according to the AJCC/UICC 2009 (for well-differentiated neoplasms), presence of metastases at diagnosis, and survival were analysed. Due to the small number of poorly differentiated neuroendocrine neoplasms, staging by the AJCC/UICC for cancers was not included in the analysis. Incidence rates and trends of incidence were calculated. Incidence rates were expressed as the number of new cases of GEPNEN per 100,000 inhabitants/year.

To compare the groups in terms of qualitative variables non-parametric tests were used: Mann-Whitney test or Kruskal-Wallis test depending on the number of groups compared. The standardisation for age was carried out with direct method using the standard European population. Trends in incidence were determined

by linear regression. Overall survival was measured from date of diagnosis until death from any cause or date of the last observation.

The Ethics Committee of the Jagiellonian University Medical College approved the study setting.

Results

Eighty-eight patients (49 [56%] females, 39 [44%] males) with GEPNEN detected between 01.01.2007 and 31.12.2011, living in Krakow or Krakow district, were identified. 75% of them were followed in the Endocrinology Department of University Hospital in Krakow. The median age at diagnosis was 59 ± 17 years.

The most common primary tumour site was small intestine (20% of cases), followed by appendix (18%), stomach (16%), pancreas (16%), rectum (15%), and colon (15%). The most common were NENG1 (64%) tumours. NENG2 and NEC comprised 28% and 8% of cases, respectively. Tumour grading was associated with tumour primary site ($p < 0.001$) (Fig. 1).

Sufficient data for staging were available in 72 (90%) patients. NENG1 and NENG2 were most commonly diagnosed at stage I (63%) and less frequently at stage II (7%), III (11%), or 0 (1%). It should, however, be stressed that 18% of cases were documented as stage IV at presentation. Staging was significantly related to tumour location (Fig. 2).

The data on the presence of metastases at the time of diagnosis were available in 80 (91%) patients. In this group disseminated disease was documented in 31% of cases. Metastases at diagnosis were significantly related to the primary tumour location ($p < 0.001$). They were most often present in colonic (67%), small intestinal (56%), and pancreatic (44%) NEN. Metastases were rare in appendiceal (0%), rectal (8%), and gastric (23%) NEN patients.

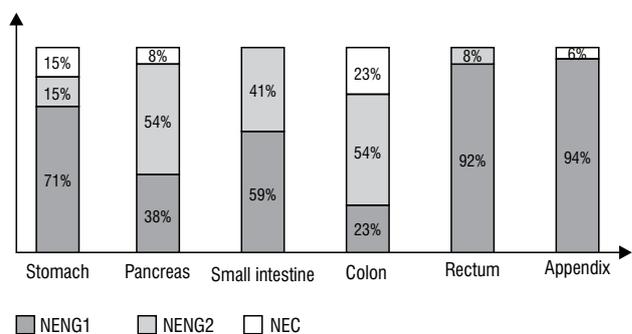


Figure 1. GEPNEN grading (the WHO 2010 classification) according to primary tumor site, $n = 87$, $p < 0.001$

Rycina 1. Stopień zróżnicowania GEPNEN (wg klasyfikacji WHO 2010) w zależności od pierwotnej lokalizacji nowotworu, $n = 87$, $p < 0,001$

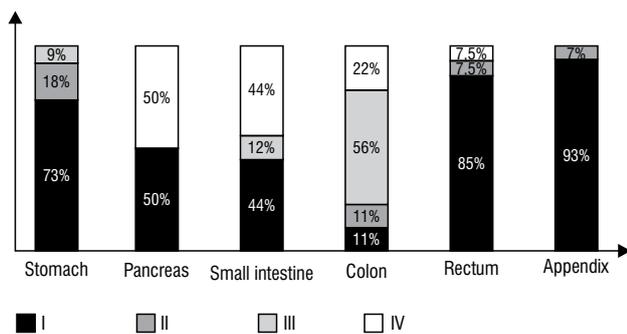


Figure 2. GEPNEN staging at diagnosis (the AJCC/UICC 2009 classification) according to primary site; $n = 72$, $p < 0.001$

Rycina 2. Stopień zaawansowania GEPNEN w momencie rozpoznania (wg klasyfikacji AJCC/UICC 2009) w zależności od pierwotnej lokalizacji nowotworu; $n = 72$, $p < 0,001$

Table I. GEPNEN raw and standardised incidence rates in 2007–2011 (with 95% confidence interval [CI])

Tabela I. Niestandardyzowana i standaryzowana częstość występowania GEPNEN w latach 2007–2011 (95% przedział ufności)

Year	GEPNEN incidence rate (/100 000 people)		
	Raw	Standardised*	95% CI*
2007	2.1	1.9	1.0-2.9
2008	1.6	1.5	0.7-2.3
2009	2.2	2.1	1.1-3.1
2010	2.8	2.7	1.6-3.8
2011	2.0	2.0	1.1-3.0
total	2.13	2.10	1.6-2.5

*standard: the European population

Loco-regional lymph node metastases and distant metastases at diagnosis were documented in 25% and 18% of patients, respectively.

After standardisation to the European population, the incidence rates did not differ significantly from the raw ones. Raw and standardised GEPNEN incidence rates are presented in Table I. Gender and place of residence did not influence GEPNEN incidence rates.

GEPNEN were more frequent in the population of 60 years and older than in younger group of 40–59 years old (Fig. 3) (incidence ratio: 4.8/100000/year, $p < 0.001$; in females 4.2, $p = 0.022$; in males 5.3, $p = 0.003$). Incidence was also higher in the group of 40–59 years old than 19–39 years old (1.8 and 0.8, respectively, $p = 0.015$; in females 2.0 and 0.9, respectively, $p = 0.071$; in males 1.6 and 0.7, respectively, $p = 0.116$).

Standardised incidence rates depending on primary tumour location are presented in Table II.

The statistical analysis of trends in incidence for GEPNEN did not show significant changes in incidence during the studied period (Fig. 4). There were no sig-

Table II. GEPNEN standardised incidence rates in 2007–2011 (with 95% CI) according to primary tumour location

Tabela II. Standaryzowana częstość występowania GEPNEN w latach 2007–2011 (95% przedział ufności) w zależności od pierwotnej lokalizacji nowotworu

Primary tumour site	Standardised incidence rate (/100 000 people)	95% CI*
Stomach	0.4	0.2–0.5
Pancreas	0.3	0.2–0.5
Small intestine	0.4	0.2–0.6
Colon	0.3	0.1–0.4
Rectum	0.3	0.1–0.5
Appendix	0.4	0.2–0.5

*standard: the European population

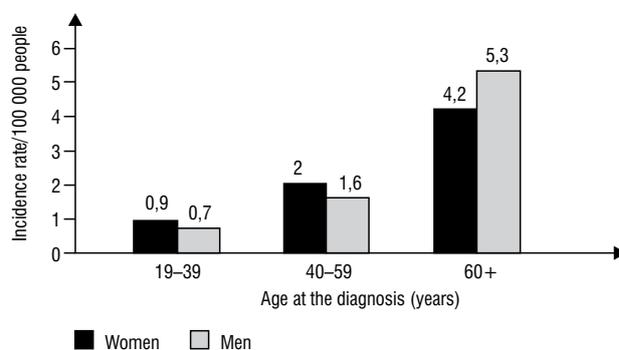


Figure 3. GEPNEN standardized incidence rates in 2007–2011 in age groups according to gender

Rycina 3. Standaryzowana częstość występowania GEPNEN w latach 2007–2011 w zależności od płci i wieku pacjentów

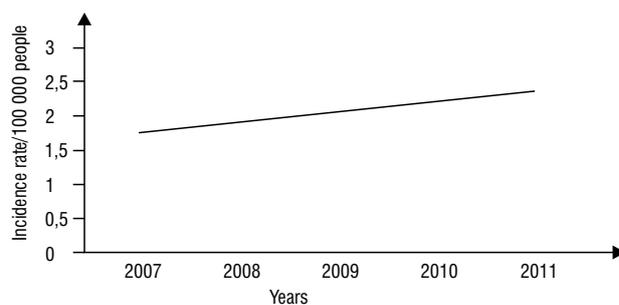


Figure 4. GEPNEN incidence trend in 2007–2011

Rycina 4. Trend częstości występowania GEPNEN w latach 2007–2011

nificant differences in trends in incidence according to age at diagnosis, gender, and place of residence.

Discussion

Most data on GEPNEN epidemiology are available for the USA or Western Europe [4]. GEPNEN epidemiologi-

cal studies are difficult due to problems with collection and comparison of data, as well as constantly changing classification systems. Relatively low ascertainment of registers, combined with the fact that sometimes they comprised only neuroendocrine cancers, may cause underestimation of GEPNEN incidence in many databases and publications [5]. The US SEER cancer registry, initiated in 1973, is the largest database of GEPNEN. Of note, up to 1986 neuroendocrine tumours were reported to the SEER database only if they were considered malignant [4].

In the study group, like in other reports [6–10], the most frequent primary location of GEPNEN was the small intestine (20% of cases). The most common were NENG1 by WHO 2010 (64% of cases), which is consistent with other studies [11–13]. NENG1 predominated among appendiceal, rectal, gastric, and small intestinal NEN. In the presented group, like in the German [14] or Korean [13] registers, well-differentiated tumours comprised the majority of cases regardless of the primary neoplasm location. Similarly to the report by Niederle et al., [11] in our series NEC comprised less than 10% of all cases.

Well-differentiated GEPNEN were diagnosed most frequently at the lowest stage (63% of cases). However, 18% of NENG1 and NENG2 were diagnosed at stage IV, and in 31% of GEPNEN metastases were present at the time of diagnosis. Similar results were presented by Niederle et al. — in the Austrian population the majority of NEN cases (65%) were diagnosed as localised disease [11]. Korse et al. noted distant metastases at diagnosis in as many as 46% of well-differentiated GEPNEN cases, which indicates the malignant potential of all GEPNEN, regardless of their grading, and the necessity of an active search for metastases even in patients with seemingly benign tumours of low grade [15].

In the presented material, appendiceal, rectal, and gastric NEN were diagnosed most commonly at the lowest stage (I). Colonic, small intestinal, and pancreatic NEN were diagnosed often as more advanced disease (stage III or IV), with metastases present in 67, 56, and 44% of cases, respectively. This is in agreement with findings from other studies [6, 8, 11]. The AJCC/UICC classification has been applied in our study to allow direct comparison of data with the largest GEPNEN database from the USA. In the SEER disseminated disease was found in most cases originating from the colon, pancreas, and small intestine; rectal, gastric, and appendiceal NEN were diagnosed mainly as a localised disease [6, 8, 11]. Similarly, in the Austrian population, Niederle et al. reported metastases in 74% of small intestinal, 70% of colonic, and 50% of pancreatic NEN, while appendiceal, rectal, and gastric NEN were most often not disseminated at diagnosis [11].

The standardised incidence rates of GEPNEN in Krakow and Krakow district in subsequent years (2007–2011) ranged from 1.5 to 2.7 per 100,000 inhabitants per year (an average of 2.1/100,000 inhabitants/year) and were lower than in the USA (3.65 in 2003–2007) [16] but similar to incidence rates reported in the large registers from other European countries (2.39 in 2004/2005 in Austria [11], 2.5 for all but pulmonary NEN in 1978–2002 in five European regions [9]) or from the Far East (1.51 in 2008 for all NEN in Taiwan [17]). A regional register from Girona in Spain (1994–2004) reported an even lower GEPNEN incidence of 1.1 [5]. The similarity of incidence rates of GEPNEN in the investigated area with other European countries indicates the good ascertainment of the Department of Endocrinology NEN register.

Like in most cancers, incidence in GEPNEN increases with age [10, 16, 18]. In our material, GEPNEN were more frequently diagnosed in subjects at least 60 years old (incidence rate of 4.8/100,000 inhabitants/year). In Tuscany NEN incidence in persons over 65 years of age was 4.3 [10], and in a register from five European regions it was 8.8 for all except pulmonary NEN [9].

In the study group standardised incidence rates in primary GEPNEN in each of the primary tumour locations ranged between 0.3 and 0.4/100,000 inhabitants/year. For comparison, in the Norwegian population they ranged from 0.16 for appendiceal to 0.81 for small intestinal NEN [7]. In smaller European registers coefficients were lower: in the province of Girona in Spain they ranged from 0.05 for gastric NEN to 0.5 for pancreatic NEN [5], and in Tuscany in Italy they were in the range 0.1–0.3 [10]. In Taiwan the primary location-specific incidence rates ranged from 0.06 for small intestinal NEN to 0.38 for rectal NEN [17]. The SEER analysis revealed higher incidence rates for small intestinal (1.08) and rectal NEN (0.97) [16].

Despite problems with registering patients, published data from large (often covering several decades) national registries show increasing incidence in GEPNEN and NEN regardless of primary tumour location in the US (except for appendiceal NEN) [8], Europe [7, 9, 19], and other geographical regions [17]. It may be partially explained by the improvement in patient registration, increased awareness of NEN among medical personnel, or progress in NEN diagnostics [4, 17]. The number of accidentally detected NEN cases rose with increasing use of various imaging techniques for other indications [20]. Hemminki et al. reported an increasing NEN incidence between 1958 and 1998; however, they emphasised that the incidence curve reached a plateau in the mid-80s, probably due to the saturation of the medical market with NEN detecting imaging techniques [19]. A smaller regional Swiss register of Vaud, covering a population of 570,000 inhabitants, revealed

increasing incidence in NEN at the end of the twentieth century, but the data comprised all NEN including lung carcinoids, which are the most common malignant neuroendocrine tumours [18]. Local European registries based on smaller populations, similar in size to that in our study (approx. 550,000 people), provide only the average incidence rates for the whole studied period, without trend analysis [5].

The statistical analysis of trends in GEPNEN incidence in Krakow and Krakow district in the years 2007–2011 did not show any significant rise, which may be related to the rarity of disease, narrowing of the analysis to patients with GEPNEN (exclusion of patients with NEN of other locations and unknown primary site), the relatively small population, and short follow-up period with available modern methods of GEPNEN diagnosis. Lack of good quality older data made it impossible to compare the results with earlier decades, as in some records (e.g. in the US SEER or large European projects [8–9]).

Conclusions

GEPNEN incidence in Krakow and Krakow district is similar to the incidence observed in most European countries. Registers are important tools to evaluate GEPNEN epidemiology.

References

- Kos-Kudła B, Blicharz-Dorniak J, Handkiewicz-Junak D, et al. Consensus Conference, Polish Network of Neuroendocrine Tumours. Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours). *Endokrynol Pol.* 2013; 64(6): 418–443, doi: [10.5603/EP.2013.0028](https://doi.org/10.5603/EP.2013.0028), indexed in Pubmed: [24431116](https://pubmed.ncbi.nlm.nih.gov/24431116/).
- Salazar R, Wiedenmann B, Rindi G, et al. ENETS 2011 Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors: an update. *Neuroendocrinology.* 2012; 95(2): 71–73, doi: [10.1159/000335600](https://doi.org/10.1159/000335600), indexed in Pubmed: [2262042](https://pubmed.ncbi.nlm.nih.gov/2262042/).
- Ramage JK, Ahmed A, Ardill J, et al. UK and Ireland Neuroendocrine Tumour Society. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut.* 2012; 61(1): 6–32, doi: [10.1136/gutjnl-2011-300831](https://doi.org/10.1136/gutjnl-2011-300831), indexed in Pubmed: [22052063](https://pubmed.ncbi.nlm.nih.gov/22052063/).
- Fraenkel M, Kim MK, Faggiano A, et al. Epidemiology of gastroenteropancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol.* 2012; 26(6): 691–703, doi: [10.1016/j.bpg.2013.01.006](https://doi.org/10.1016/j.bpg.2013.01.006), indexed in Pubmed: [23582913](https://pubmed.ncbi.nlm.nih.gov/23582913/).
- Alsina M, Marcos-Gragera R, Capdevila J, et al. Neuroendocrine tumors: a population-based study of incidence and survival in Girona Province, 1994–2004. *Cancer Epidemiol.* 2011; 35(6): e49–e54, doi: [10.1016/j.canep.2011.05.011](https://doi.org/10.1016/j.canep.2011.05.011), indexed in Pubmed: [21840785](https://pubmed.ncbi.nlm.nih.gov/21840785/).
- Yao JC, Hassan M, Phan A, et al. One hundred years after „carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008; 26(18): 3063–3072, doi: [10.1200/JCO.2007.15.4377](https://doi.org/10.1200/JCO.2007.15.4377), indexed in Pubmed: [18565894](https://pubmed.ncbi.nlm.nih.gov/18565894/).
- Hauso O, Gustafsson BI, Kidd M, et al. Neuroendocrine tumor epidemiology: contrasting Norway and North America. *Cancer.* 2008; 113(10): 2655–2664, doi: [10.1002/cncr.23883](https://doi.org/10.1002/cncr.23883), indexed in Pubmed: [18853416](https://pubmed.ncbi.nlm.nih.gov/18853416/).
- Tsikitis VL, Wertheim BC, Guerrero MA. Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: a seer analysis. *J Cancer.* 2012; 3: 292–302, doi: [10.7150/jca.4502](https://doi.org/10.7150/jca.4502), indexed in Pubmed: [22773933](https://pubmed.ncbi.nlm.nih.gov/22773933/).
- van der Zwan JM, Trama A, Otter R, et al. RARECARE WG. Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project. *Eur J Cancer.* 2013; 49(11): 2565–2578, doi: [10.1016/j.ejca.2013.02.029](https://doi.org/10.1016/j.ejca.2013.02.029), indexed in Pubmed: [23541566](https://pubmed.ncbi.nlm.nih.gov/23541566/).
- Caldarella A, Crocetti E, Paci E. Distribution, incidence, and prognosis in neuroendocrine tumors: a population based study from a cancer registry. *Pathol Oncol Res.* 2011; 17(3): 759–763, doi: [10.1007/s12253-011-9382-y](https://doi.org/10.1007/s12253-011-9382-y), indexed in Pubmed: [21476126](https://pubmed.ncbi.nlm.nih.gov/21476126/).
- Niederle MB, Hackl M, Kaserer K, et al. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer.* 2010; 17(4): 909–918, doi: [10.1677/ERC-10-0152](https://doi.org/10.1677/ERC-10-0152), indexed in Pubmed: [20702725](https://pubmed.ncbi.nlm.nih.gov/20702725/).
- Lim T, Lee J, Kim JJ, et al. Gastroenteropancreatic neuroendocrine tumors: incidence and treatment outcome in a single institution in Korea. *Asia Pac J Clin Oncol.* 2011; 7(3): 293–299, doi: [10.1111/j.1743-7563.2011.01423.x](https://doi.org/10.1111/j.1743-7563.2011.01423.x), indexed in Pubmed: [21884442](https://pubmed.ncbi.nlm.nih.gov/21884442/).
- Cho MY, Kim JM, Sohn JH, et al. Gastrointestinal Pathology Study Group of Korean Society of Pathologists. Current Trends of the Incidence and Pathological Diagnosis of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) in Korea 2000–2009: Multicenter Study. *Cancer Res Treat.* 2012; 44(3): 157–165, doi: [10.4143/crt.2012.44.3.157](https://doi.org/10.4143/crt.2012.44.3.157), indexed in Pubmed: [23091441](https://pubmed.ncbi.nlm.nih.gov/23091441/).
- Ploekinger U, Kloepffel G, Wiedenmann B, et al. representatives of 21 German NET Centers. The German NET-registry: an audit on the diagnosis and therapy of neuroendocrine tumors. *Neuroendocrinology.* 2009; 90(4): 349–363, doi: [10.1159/000242109](https://doi.org/10.1159/000242109), indexed in Pubmed: [19776553](https://pubmed.ncbi.nlm.nih.gov/19776553/).
- Hubalewska-Dydejczyk A, Trofimiuk M. Diagnostic and therapeutic management of neuroendocrine tumors of unknown origin. In: Kos-Kudła B, ed. *Gastroenteropancreatic neuroendocrine tumors*. Hubalewska-Dydejczyk A, Trofimiuk M. ed. Via Medica, Gdańsk : 325–342.
- Lawrence B, Gustafsson BI, Chan A, et al. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am.* 2011; 40(1): 1–18, vii, doi: [10.1016/j.ecl.2010.12.005](https://doi.org/10.1016/j.ecl.2010.12.005), indexed in Pubmed: [21349409](https://pubmed.ncbi.nlm.nih.gov/21349409/).
- Tsai HJ, Wu CC, Tsai CR, et al. The epidemiology of neuroendocrine tumors in Taiwan: a nation-wide cancer registry-based study. *PLoS One.* 2013; 8(4): e62487, doi: [10.1371/journal.pone.0062487](https://doi.org/10.1371/journal.pone.0062487), indexed in Pubmed: [23614051](https://pubmed.ncbi.nlm.nih.gov/23614051/).
- Levi F, Te VC, Randimbison L, et al. Epidemiology of carcinoid neoplasms in Vaud, Switzerland, 1974–97. *Br J Cancer.* 2000; 83(7): 952–955, doi: [10.1054/bjoc.2000.1394](https://doi.org/10.1054/bjoc.2000.1394), indexed in Pubmed: [10970700](https://pubmed.ncbi.nlm.nih.gov/10970700/).
- Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. *Cancer.* 2001; 92(8): 2204–2210, indexed in Pubmed: [11596039](https://pubmed.ncbi.nlm.nih.gov/11596039/).
- Zárate X, Williams N, Herrera ME. Pancreatic incidentalomas. *Best Pract Res Clin Endocrinol Metab.* 2012; 26(1): 97–103, doi: [10.1016/j.beem.2011.06.005](https://doi.org/10.1016/j.beem.2011.06.005), indexed in Pubmed: [22305455](https://pubmed.ncbi.nlm.nih.gov/22305455/).