ORIGINAL ARTICLE

Gastroenteropancreatic neuroendocrine neoplasms: a 10-year experience of a single center

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KEY WORDS

clinical features, gastroentreopancreatic neuroendocrine neoplasms, survival

ABSTRACT

INTRODUCTION Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) constitute a rare and heterogeneous group of tumors with varied biology.

OBJECTIVES The aim of this study was to establish the clinical characteristics of patients with GEP-NEN and identify factors influencing their 5-year survival.

PATIENTS AND METHODS The study included 122 patients living in Kraków or its administrative region, who were diagnosed with GEP-NEN between 2002 and 2011.

RESULTS The mean follow-up period was 4.9 ±2.8 years. The most frequent primary site of the tumor was the small intestine (n = 25; 20%), followed by pancreas (n = 23; 19%), rectum (n = 23; 19%), stomach (n = 21; 17%), appendix (n = 19; 16%), and colon (n = 11; 9%). There were 84 tumors classified as NEN G1; 31, as NEN G2; 5, as neuroendocrine carcinoma; and 1, as mixed adenoneuroendocrine carcinoma. Most well-differentiated GEP-NENs (n = 57; 57%) were diagnosed at stage I according to the American Joint Committee on Cancer / Union for International Cancer Control (AJCC/UICC) classification; 77% of NEN G1 (n = 64) were diagnosed at stage I, but the majority of NEN G2—at stage IV (n = 18; 58%). Metastases at diagnosis were found in 38 patients (34%). In 90% of the cases (n = 101), tumors were hormonally nonfunctional. The overall 5-year survival was 85%. In the univariate analysis, NEN G2 ($P = 0.003$), higher stage according to the AJCC/UICC classification ($P < 0.001$), and metastases at diagnosis ($P < 0.001$) were associated with poorer prognosis. In standardized multivariate models, higher stage ($P = 0.02$) and metastases at diagnosis ($P = 0.02$) were independent risk factors for death.

CONCLUSIONS The most important factors affecting survival of patients with GEP-NENs are tumor stage and the presence of metastases at diagnosis. The analysis of single-center data improves identification of patients with poorer prognosis requiring a more aggressive approach.

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INTRODUCTION Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) still constitute a diagnostic and therapeutic challenge for physicians of all specialties. GEP-NENs are a highly heterogeneous and poorly understood group of rare but increasingly prevalent tumors with varied clinical presentation. They may present as relatively indolent but also as highly aggressive and rapidly metastasizing tumors.[1-3]

As a malignant transformation of diffuse endocrine cells, GEP-NENs are capable of synthesizing and secreting hormones. Most GEP-NENs, however, are nonfunctioning and are not related to specific symptoms, which makes an early diagnosis challenging,[4-6] reduces the chances of curative surgery, and decreases patient survival.[7]

Apart from early diagnosis, an important component of proper management is the ability to

TABLE 1 Clinical characteristics of the study group

Characteristics	n (%)
sex	
female	69 (57)
male	53 (43)
primary tumor site	
stomach	21 (17)
pancreas	23 (19)
small intestine	25 (20)
colon	11 (9)
rectum	23 (19)
appendix	19 (16)
WHO classification, 2010	
NEN G1	84 (69)
NEN G2	31 (26)
NEC	5 (4)
MANEC	1 (1)
AJCC/UICC classification, 2009	
0	3 (3)
I	57 (57)
II	10 (9)
III	10 (9)
IV	22 (22)
other neoplasms	9 (16)
hormonal activity	
nonfunctioning NEN	101 (90)
functioning NEN	11 (10)
typical carcinoid	1 (1)
functioning pancreatic NEN	10 (9)
treatment	
surgical	107 (95)
somatostatin analogs	24 (24)
radionuclide treatment	20 (20)
chemotherapy	8 (8)
treatment of liver metastases	20 (95)
other (thyrosine kinase inhibitor, diazoxide)	2 (2)

Abbreviations: AJCC/UICC, American Joint Committee on Cancer / Union for International Cancer Control; MANEC, mixed adenoneuroendocrine carcinoma; NEC, neuroendocrine cancer; NEN, neuroendocrine neoplasm; WHO, World Health Organization

stratify patients into prognostic groups. However, this has been limited by the absence of commonly accepted classifications.[8] In the last decade, attempts to unify the available classification systems have been made. The 2010 World Health Organization (WHO) classification of NENs based on the Ki67 proliferative index and mitotic count has provided clinically relevant and prognostically useful criteria; however, it has not been adopted worldwide and has been applied only in a few studies. Current staging systems developed by the American Joint Committee on Cancer / Union for International Cancer Control (AJCC/UICC) in 2009 or by the European Neuroendocrine Tumor Society (ENETS) in 2006 and 2007, both based on the TNM scoring system (Tumor size, Lymph Nodes affected, Metastases), differ substantially and may result in confusion because they use the same nomenclature.[9,10] Therefore, the comparison of data from different centers becomes difficult or impossible.[11]

Furthermore, data on long-term follow-up and survival in patients with GEP-NEN are limited. There are only a few analyses of prognostic factors that might allow to identify high-risk factors, partially due to discrepancies in diagnosis and rarity of these tumors.[12] Epidemiological data based on large registry databases may not provide details on the clinical and pathological features and natural history of GEP-NEN.[13] A few reports concerning predicting survival and disease progression have been published so far; however, the prognostic factors for GEP-NEN are complex, multifaceted, and have not been clearly defined so far.[14,15] Data from many countries on the survival of patients with GEP-NEN and factors affecting survival are lacking.[16] This implies the need for further studies on prognostic parameters.[17]

In this study, we evaluated the prognostic significance of several routinely used parameters in a single-center series of patients with GEP-NENs.

PATIENTS AND METHODS

The study included 122 patients (69 women, 53 men) identified from the database of the Department of Endocrinology, University Hospital in Kraków, comprising 341 subjects, mostly from south-eastern Poland, diagnosed with GEP-NEN between January 2002 and December 2011. The inclusion criteria were as follows: residency in the administrative region of Kraków and histologically confirmed and verified GEP-NEN with sufficient data to stratify the patient according to the currently used classifications. We recorded clinical and pathological parameters including age, sex, primary tumor location, grading (according to the WHO 2010 criteria), staging (according to the AJCC/UICC 2009 criteria for well-differentiated tumors), distant and locoregional lymph node metastases at diagnosis, hormonal activity, main symptoms, and simultaneous presence of other neoplasms.

Associations between various clinical and pathological characteristics and probability of 5-year overall survival were assessed with the χ^2 or Fisher exact tests. Overall survival was measured from the date of diagnosis until death from any cause. The 5-year Kaplan–Meier survival curves were constructed for each variable. For a multivariate analysis, relative risks with 95% confidence intervals were calculated using Cox proportional hazard models. All analyses were conducted with the Stata 12.1 software (StataCorp LP, College Station, Texas, United States). A *P* value of less than 0.05 was considered statistically significant.

The study was approved by the Ethics Committee of the Jagiellonian University in Kraków.

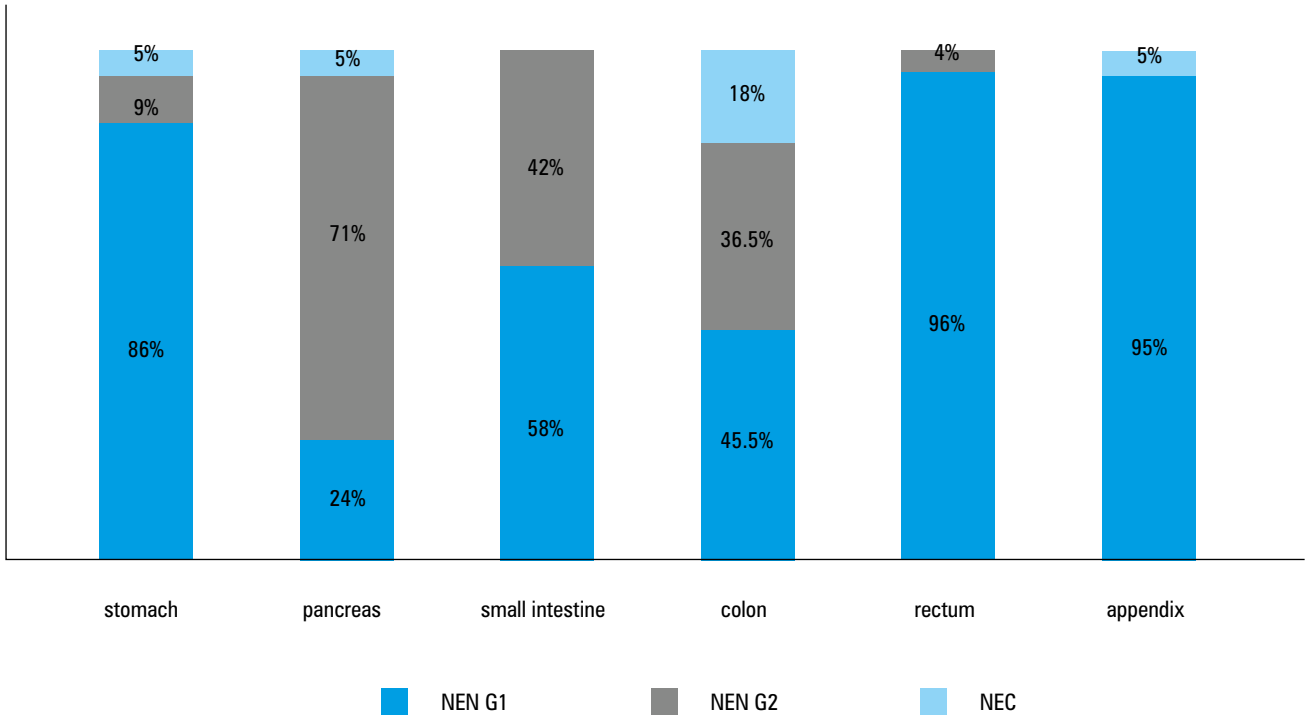

FIGURE 1 Distribution of gastroenteropancreatic neuroendocrine neoplasms (World Health Organization classification, 2010, n = 121) according to primary tumor site
Abbreviations: see **TABLE 1**

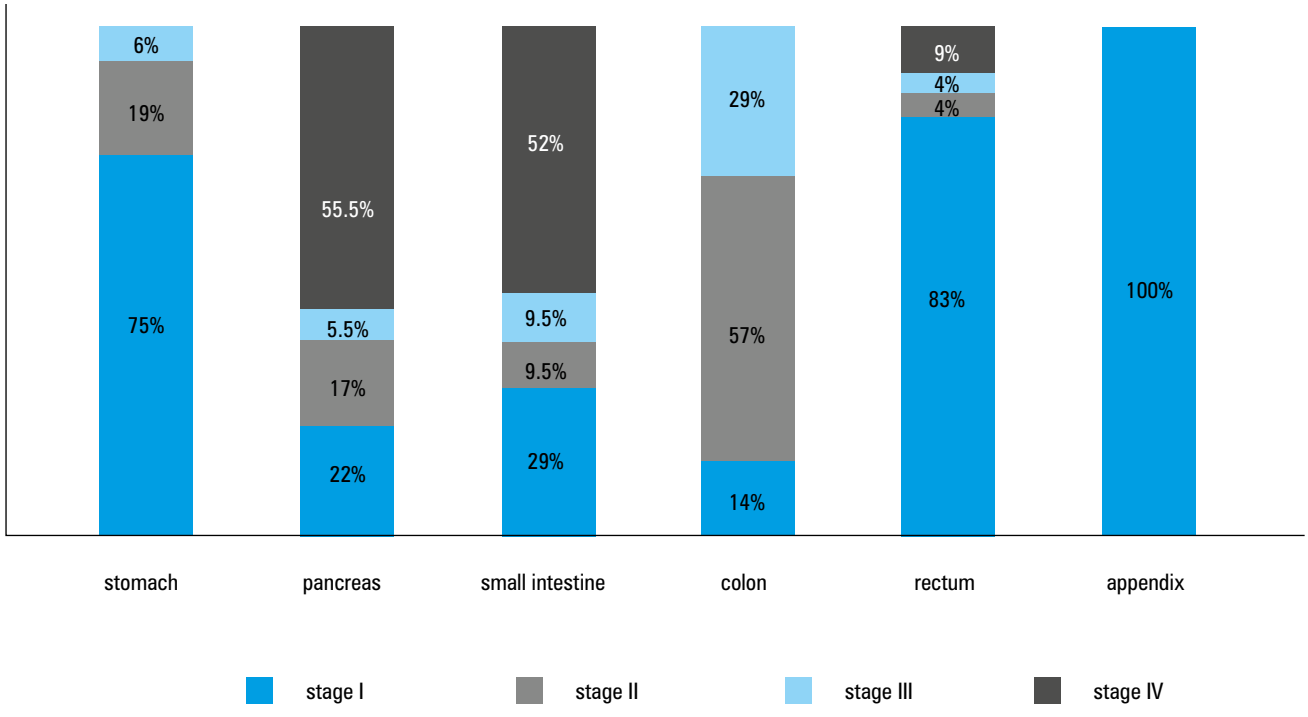

FIGURE 2 Distribution of gastroenteropancreatic neuroendocrine neoplasms (American Joint Committee on Cancer / Union for International Cancer Control classification, 2009, n = 102) according to primary tumor site

RESULTS Clinical characteristics of the study group are presented in **TABLE 1**.

The mean age at diagnosis was 57 ±15 years and correlated with the primary site of the tumor (P = 0.03): patients with appendiceal NENs (mean, 44 ±21 years) were the youngest and those with small bowel and pancreatic NENs—the oldest (>60 years).

The most common primary tumor site was the small intestine (n = 25; 20%), followed by the pancreas (n = 23; 19%), rectum (n = 23; 19%), stomach (n = 21; 17%), appendix (n = 19; 16%), and colon (n = 11; 9%). There was no significant correlation between tumor site and sex.

A total of 121 GEP-NENs (99%) were classified according to the 2010 WHO criteria. NEN G1

TABLE 2 Clinical features according to the primary tumor site among patients with nonfunctioning tumors

Symptom	All (n = 101)	Stomach (n =18)	Pancreas (n = 13)	Small intestine (n = 23)	Colon (n = 9)	Rectum (n = 20)	Appendix (n = 18)	*P* value
fever	1	6	0	0	0	0	0	0.57
syncope	1	0	0	4	0	0	0	1.0
excessive sweating	1	0	0	0	11	0	0	0.09
heartburn	2	6	0	0	0	0	6	0.6
jaundice	2	0	0	9	0	0	0	0.4
appetite loss	3	6	8	4	0	0	0	0.78
flush	3	11	0	0	0	0	0	0.5
vomiting	4	0	15	4	0	0	0	0.29
nausea	7	0	23	9	0	10	0	0.1
weakness	9	0	15	13	11	5	6	0.8
anemia	11	39	8	4	0	5	6	0.01
constipation	11	17	0	13	11	15	6	0.69
diarrhea	12	17	8	13	0	20	6	0.68
weight loss	14	17	15	22	11	5	11	0.7
gastrointestinal blood loss	16	6	0	22	44	30	0	0.003
abdominal distention / belching	18	28	8	26	0	30	0	0.03
acute abdominal pain	21	0	8	22	22	0	67	<0.001
chronic abdominal pain	43	50	77	52	44	30	11	0.005
abdominal pain	57	50	77	65	44	30	78	0.03
no symptoms	11	11	15	4	22	6	15	0.8

Data are presented as percentages.

were the most common (n = 84; 69%). NEN G2, neuroendocrine carcinoma (NEC), and mixed adenoneuroendocrine carcinoma constituted 26% (n = 31), 4% (n = 5), and 1% (n = 1) of the tumors, respectively. Tumor grading according to the WHO classification was strongly associated with the primary tumor site (P <0.001; FIGURE 1). There was no significant difference in tumor grading in terms of sex.

Sufficient data for staging according to the AJCC/UICC classification (for well-differentiated tumors) were available in 102 of 115 patients (89%) with NEN G1 and G2. Patients were most commonly diagnosed with stage I tumors (n = 57; 57%), but almost one-fourth of the cases (n = 22; 22%) had stage IV tumors at presentation. Stages 0, II, and III constituted 3% (n = 3), 9% (n = 10), and 9% (n = 10) of the tumors, respectively. NEN G1 were most frequently diagnosed at stage I (n = 64; 77%) and NEN G2—at stage IV (n = 18; 58%) (P <0.001; additional data are presented in Supplementary material online, *Figure S1*). Staging was significantly related to sex and tumor site. Women (n = 59) were diagnosed at earlier stages than men (n = 43) (stage I or II: 75% and 55%; stage III or IV: 25% and 45%, respectively; P = 0.038). The AJCC/UICC staging of GEP-NENs according to the primary tumor site is presented in FIGURE 2 (P <0.001). Three patients with NEC were diagnosed at stage II (colonic, pancreatic, and appendiceal NECs); 1 patient with colonic NEC, at stage III; and 1 patient with gastric NEC, at stage IV.

At the time of diagnosis, information on the presence or lack of metastases was available in 112 patients (92%), of whom 38 (34%) had disseminated disease. Metastases at diagnosis were more often present in men than in women (44% vs. 27%, P = 0.057). The highest percentage of metastatic disease was noted for colonic (n = 7; 78%), pancreatic (n = 13; 62%), and small intestinal (n = 13; 62%) NENs, while among gastric or rectal NENs, metastases were found only in a few cases (n = 2; 11% and n = 3; 13%, respectively). All of the appendiceal NENs (n = 19) were diagnosed as localized disease (P <0.001). Locoregional lymph node metastases were identified in 29 patients (26%), mainly in colonic (n = 7; 78%), small intestinal (n = 11; 52%), and pancreatic (n = 7; 33%) NENs (P <0.001). Distant metastases at diagnosis were found in 22% of the cases (n = 25), most often in pancreatic (n = 10; 48%) and small intestinal (n = 10; 48%) NENs (P <0.001). Most NEN G1 (n = 65; 86%) were diagnosed as localized disease, and most NEN G2 (n = 23; 79%)—as metastatic tumors. Among patients with NEC, metastases were present in 40% (n = 2; P <0.001).

In 1 patient with pancreatic NEN, MEN 1 syndrome was reported. One patient with rectal NEN was diagnosed with neurofibromatosis type 1. Other concurrent neoplasms were observed in 9 of 121 patients (16%) (Supplementary material online, *Figure S2*).

Data on hormonal activity were obtained in 112 patients (92%). Hormone-related syndromes were detected in 11 patients: in 1 patient with

TABLE 3 Factors associated with 5-year overall survival according to the univariate Cox proportional hazard model (n = 122)

		Relative risk of death	95% confidence interval	*P* value
sex	men	1.0		
	women	0.73	0.29–1.85	0.5
place of residency	Kraków city	1.0		
	Kraków region	1.78	0.45–4.19	0.57
time of diagnosis	2002–2004	1.0		
	2005–2007	1.13	0.29–4.36	0.86
	2008–2011	1.56	0.41–5.98	0.5
age at diagnosis, y	19–39	1.0		
	40–59	1.48	0.3–7.32	0.6
	≥60	1.68	0.37–7.69	0.5
2010 WHO classification	NEN G1	1.0		
	NEN G2	4.53	1.65–12.47	0.003
	NEC	2.99	0.36–24.92	0.3
2009 AJCC/UICC classification	stage I	1.0		
	stage II[a]	–	–	–
	stage III	2.2	0.23–21.17	0.49
	stage IV	10	2.89–37.24	<0.001
metastases	no	1.0		
	Yes	7.08	2.31–21.73	0.001
regional lymph node metastases	No	1.0		
	Yes	4.53	1.72–11.92	0.002
distant metastases	No	1.0		
	Yes	5.73	2.18–15.08	<0.001
primary tumor site	appendix	1.0		
	stomach[a]	–	–	–
	pancreas	1.81	0.33–9.89	0.49
	small intestine	3.02	0.63–14.62	0.17
	colon	2.96	0.49–18.03	0.2
	rectum	0.72	0.1–5.14	0.7

a no deaths in the group

Abbreviations: see TABLE 1

colonic NEN, who developed typical carcinoid syndrome, and in 10 patients (43%) with pancreatic NEN (5 insulinomas, 4 glucagonomas, and 1 VIPoma). Nonfunctioning tumors were significantly more common in the group, accounting for 90% of NEN (n = 101; *P* <0.001). Abdominal pain, mainly chronic, was the most common complaint (57% of 101 cases). Clinical features among 101 patients with nonfunctioning tumors correlated with the primary tumor site (TABLE 2).

Eleven patients (11%) with nonfunctioning tumors were asymptomatic. All these 11 tumors were diagnosed as well-differentiated NENs (7 NEN G1, 64%; 4 NEN G2, 36%), mostly at early stages (n = 6; 60% at stage I) with localized disease (n = 7; 64%). However, 20% of asymptomatic cases (n = 2) were diagnosed at stage IV.

The mean follow-up period was 4.9 ±2.8 years. The observed 5-year overall survival was 85%. There was no significant correlation between survival and tumor site, age, sex, place of residency, and year of diagnosis (compared periods: 2002–2004, 2005–2007, and 2008–2011). Diagnosis of NEN G1 was associated with the best prognosis, with the observed 5-year overall survival of 93% (*P* = 0.004). Patients with stages I or II tumors performed better than those with stages III or IV (96% vs 65%, respectively, *P* <0.001). The 5-year overall survival rates depending on the presence or lack of metastases were 66% and 95%, respectively (*P* <0.001). The site-specific 5-year overall survival rates were 100% for the appendix, 91% for the rectum, 89% for the stomach, 83% for the pancreas, 73% for the colon, and 72% for the small intestine (*P* = 0.06). In the univariate analysis, higher stage (*P* <0.001), NEN G2 (*P* = 0.003), and metastases at diagnosis (*P* <0.001) were associated with poorer prognosis (TABLE 3, FIGURES 3 and 4, Supplementary material online, *Figure S3*). In standardized multivariate models, adjusted for sex, age, and place of residency, higher stage (*P* = 0.02) and metastases (*P* = 0.02) were the independent risk factors for poor outcome (TABLE 4).

DISCUSSION Most epidemiological data on GEP-NEN come from the United States or Western Europe. To our best knowledge, the present study is the first to report clinical and pathological features as well as prognostic factors for GEP-NENs in Eastern Europe. The lack of stable and uniform nomenclature and classification systems and common underreporting of NEN make it difficult to compare different databases. Many publications based on cancer registries do not include benign or indolent tumors.[11]

In our study, the average age at diagnosis was 57 years, which is consistent with other reports.[17-20] Similarly to other studies, there were significant differences in the average age at diagnosis depending on the primary tumor site. Appendiceal NEN were diagnosed in the youngest patients,[2,18,21-22] probably due to an incidental discovery of the neoplasm during appendectomy for other indications.[23]

As in most other reports from Europe and the United States, the most common primary tumor site in our series was the small intestine.[2,12,18,21,24-30] However, in Asian epidemiological surveys, rectal NENs were more frequent.[5] The Surveillance, Epidemiology, and End Results Program, the largest American cancer database, revealed a 1.5- to 3-fold higher incidence of rectal NEN in African-Americans than in Caucasians.[18] This discrepancy in organ distribution may suggest ethnic differences in the development of GEP-NEN, although there is no scientific evidence to support this hypothesis.

In the present group, low grade NENs (G1 according to the 2010 WHO classification) were the most common, which is consistent with other studies.[5,17,22,31] NEN G1 predominated in the rectum, appendix, stomach, small intestine, and colon, similarly to German[19] and Korean[17] registries,

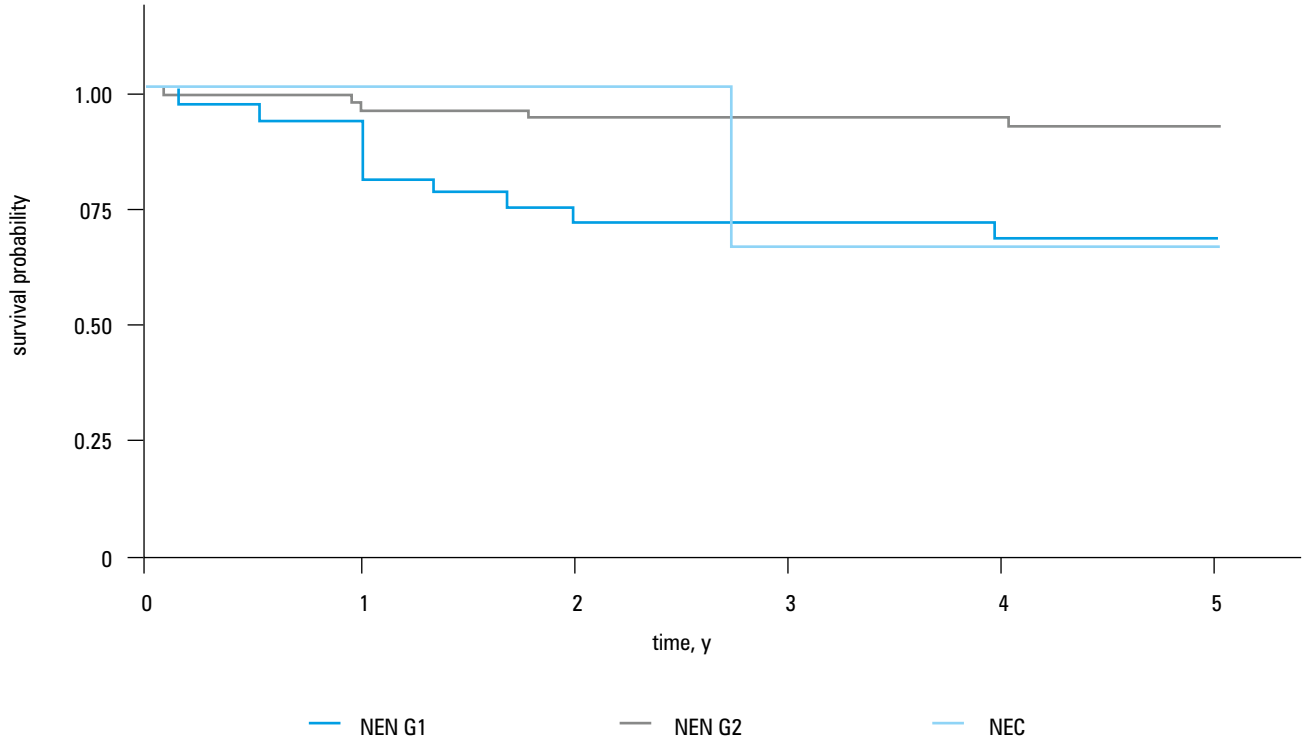

FIGURE 3 Kaplan–Meier 5-year overall survival curves according to the World Health Organization 2010 classification; log-rank test for equality of survivor functions ($P = 0.007$)
Abbreviations: see **TABLE 1**

TABLE 4 Multivariate analyses of factors associated with 5-year overall survival: 2 different Cox proportional hazard models including patient's age, sex, place of residency, tumor grading, and staging (model A) or metastases (model B)

		Relative risk of death	95% confidence interval	*P* value
model A				
age at diagnosis	unit = 10 years	1.23	0.74–2.04	0.4
sex	women/men	1.79	0.5–6.39	0.37
place of residency	Kraków district / Kraków city	3.58	0.88–14.55	0.08
2009 AJCC/UICC classification	stage II/stage I[a]	–	–	–
	stage III/stage I	2.73	0.24–30.77	0.4
	stage IV/stage I	10.39	1.41–76.36	0.02
2010 WHO classification	NEN G2/NEN G1	0.95	0.18–5.1	0.95
	NEC/NEN G1	2.29	0.21–25.08	0.5
model B				
age at diagnosis	unit = 10 years	1.15	0.77–1.72	0.48
sex	women/men	1.44	0.5–4.22	0.5
place of residency	Kraków district / Kraków city	2.1	0.62–7.13	0.2
metastases	yes/no	6.33	1.43–28.1	0.02
2010 WHO classification	NEN G2/NEN G1	1.16	0.3–4.51	0.8
	NEC/NEN G1	1.46	0.17–12.63	0.7

a no deaths among patients with stage II NENs

Abbreviations: see **TABLE 1**

in which well-differentiated tumors comprised the majority of cases regardless of the primary tumor site. Similarly to the study by Niederle et al.,[22] in our series, NEC constituted less than 10% of all cases.[22]

Most of well-differentiated GEP-NENs (57%) were diagnosed at stage I according to the AJCC/UICC classification. In the examined group, 77% of the cases with NEN G1 were diagnosed at stage I; however, the majority (58%) of NEN G2—at stage IV. Approximately in 30% of the patients, dissemination of the disease was confirmed at diagnosis. Similar results were presented by Niederle et al.[22] in the Austrian population,

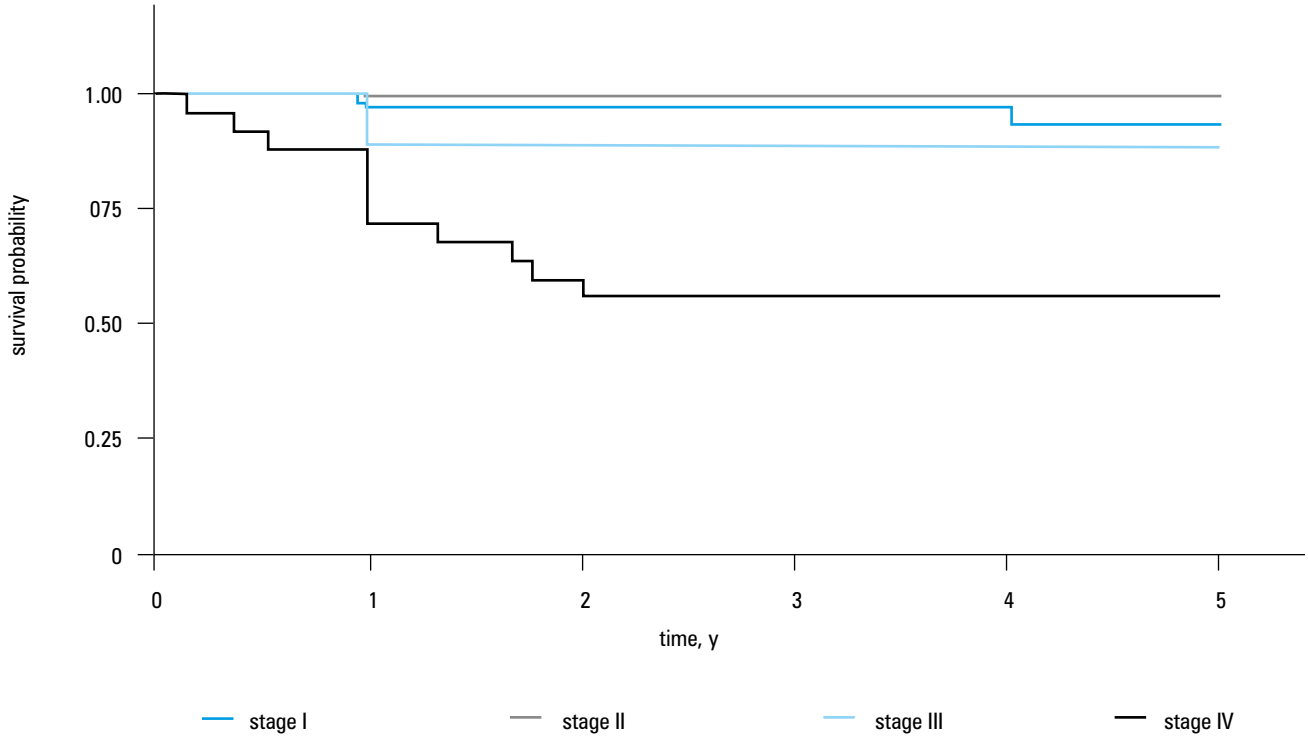

FIGURE 4 Kaplan–Meier 5-year overall survival curves according to the 2009 American Joint Committee on Cancer / Union for International Cancer Control classification; log-rank test for equality of survivor functions (P <0.001)

where the majority of patients with NENs (65%) had localized disease, but dissemination was revealed in 35% of the patients and the presence of distant metastases—in 24% (ENETS stage IV is similar to the AJCC/UICC classification). Disseminated disease was found in most patients with GEP-NENs originating from the colon, pancreas, and small intestine. Rectal, gastric, and appendiceal NENs were diagnosed mainly as localized disease, which is in agreement with the findings from other studies.[2,21-22,31-32] In our study, women were diagnosed at earlier stages than men, which may be related to a more frequent use of medical services by women, including diagnostic tests. However, literature data on this subject are inconsistent.[2,20-22,24] The above results contradict the previous notion that all GEP-NENs are indolent and benign.

GEP-NENs are associated with a higher risk of developing other neoplasms, probably owing to the genetic background or tumor growth factor secretion by NENs.[1,4] In our study, the coexisting neoplasms, mostly gastrointestinal non-neuroendocrine cancers, were found in 16% of the patients. In the literature, the coincidence of other tumors with GEP-NEN ranges from 10% to 32%,[7,14,18,33-34] with a similar predominance of gastrointestinal malignancy. These data emphasize the need for more detailed cancer screening in all patients with GEP-NEN.

In most cases, the symptoms of NENs are nonspecific, caused by compression or invasion of certain structures by the primary tumor or metastases.[4,35] As in other studies, most of GEP-NENs in our database were nonfunctioning.[4,36-37] Similarly to the studies by Shebani et al.[7] and Helland et al.,[27] the most common symptom of nonfunctioning NENs was abdominal pain (60% of the patients), mainly chronic pain. In our study, as in that by Shebani et al.,[7] the prevalence of pain as the leading symptom depended on the primary site of the tumor and ranged from 30% in rectal NENs to 77% in pancreatic NENs, which is caused by different pathophysiology of the symptom.

About 10% of the patients in our group were asymptomatic and GEP-NEN was diagnosed accidentally. Although in 60% of asymptomatic cases, the disease was diagnosed in the early stages, in 20% of them, distant metastases were found at diagnosis. Similarly, Shebani et al.[7] reported the presence of regional lymph node or liver metastases in approximately 20% of the patients with incidentally diagnosed GEP-NEN.

In our study, the 5-year overall survival was 85%, which is consistent with other studies (67%–90%).[5,11,28,38-39] If only malignant NENs are considered, the prognosis is substantially worse (5-year survival of 40%–60%).[12,40-41] Because an unknown primary location (with documented worse prognosis)[13,28,31,42] may indicate a NEN of other than the gastroenteropancreatic origin, we excluded such patients from our analysis. GEP-NENs, although no longer considered benign tumors,[18] are still characterized by better prognosis and longer survival than most other digestive tract cancers (the median overall survival in small bowel adenocarcinomas is 36.6 months).[40,43]

The univariate survival analysis demonstrated worse prognosis with a higher stage, intermediate grade (NEN G2), and metastases at diagnosis, confirming literature data on the association between the length of survival and both the extent of the

disease at diagnosis and the histopathological type of the tumor.[5,7,12,14,17,18,21,24-26,28,31,38,40-42,44-46] In our group, metastatic disease was related to a 7-fold higher risk of death. The 5-year survival for stages I and IV neoplasms in our group was similar to those reported in other studies: 95% and 56%, respectively, in our study; 92% and 57% according to Strosberg et al.[8]; and 93% and 56% according to Ellison et al.[47] In a study by Chapgar et al.,[48] it was 91% and only 25%, respectively.[48] In our analysis, the risk of death in patients with NEN G2 was 5 times higher than in those with NEN G1. The higher grade was associated with worse prognosis also in other studies.[44,49,50] The 5-year survival rates were 96% for G1, 73% for G2, and 28% for G3 according to Pappe et al.[44] and 95% for G1, 82% for G2, and 51% for G3 according to Jann et al.[50] In our study, there was no statistically significant difference in the risk of death between patients with NEC and NEN G1, most probably owing to a small nonrepresentative number of patients with NEC.

Numerous studies have shown different survival rates depending on tumor location.[2,5,11,12,17,18,20,21,24-28,38,40-42,45,46,51] In our study, similarly to the German registry,[19] the 5-year survival depended on the primary tumor site; however, the difference did not reach significance. The highest 5-year survival rate was observed in the case of appendiceal (100%), rectal (91%), and gastric (89%) NENs and the lowest—among patients with colonic (73%), small intestinal (72%), and pancreatic (83%) NENs. Other reports confirm the best prognosis in rectal or appendiceal NENs.[11,18-20,24-25,27-28,42]

In our group, as in the reports by Helland et al.[27] and Lim et al.,[5] mortality in GEP-NEN did not differ according to sex. Other reports, including a summary of the Surveillance, Epidemiology, and End Results Program, showed longer survival rates among women than among men.[7,12,20,21,28,40,41,45] The difference might have been caused by the sample size because in our study women were also more frequently diagnosed at stages I and II than men. Other factors that did not noticeably influence patients' outcome in the current study were the place of residence and year of diagnosis. However, the administrative region of Kraków is a relatively small area of about 1500 km^2.

In standardized multivariate models, high stage and metastases were the independent risk factors for poor outcome. In the examined models in our series, grading was a weak predictor of mortality, which may result from a small number of patients with NEC. According to Garcia-Carbonaro et al.,[28] independent risk factors of fatal outcome are grading and staging at diagnosis. Lim et al.[5] also reported primary tumor location as an independent risk factor for death, with poorer prognosis for hepatobiliary NEN.

Contribution statement EL, MT-M, DP, and AH-D conceived the idea of the study and contributed to the design of the research. All authors were involved in data collection. KW and RT contributed to correct pathological classification of the data. AK, DP, EL, and MT-M contributed to the statistical analysis of the data. All authors edited and approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Nowotwory neuroendokrynne układu pokarmowego – 10-letnie doświadczenie jednego ośrodka

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SŁOWA KLUCZOWE

nowotwory neuroendokrynne układu pokarmowego, objawy, przeżywalność

STRESZCZENIE

WPROWADZENIE Nowotwory neuroendokrynne układu pokarmowego (*gastroenteropancreatic neuroendocrine neoplasms* – GEP-NEN) stanowią rzadką i heterogenną grupę guzów o zróżnicowanej biologii.
CELE Celem niniejszego badania była charakterystyka kliniczna pacjentów z GEP-NEN i wyłonienie czynników wpływających na ich 5-letnią przeżywalność.
PACJENCI I METODY Do badania włączono 122 pacjentów z GEP-NEN rozpoznanymi w latach 2002–2011, zamieszkujących w Krakowie lub powiecie krakowskim.
WYNIKI Średni czas obserwacji wynosił 4,9 ± 2,8 roku. Najczęstszą lokalizacją ogniska pierwotnego było jelito cienkie (n = 25; 20%), następnie trzustka (n = 23; 19%), odbytnica (n = 23; 19%), żołądek (n = 21; 17%), wyrostek robaczkowy (n = 19; 16%) i jelito grube (n = 11; 9%). W badanej grupie wystąpiły 84 guzy NEN G1, 31 guzów NEN G2, 5 guzów NEC oraz 1 guz MANEC. Większość wysoko zróżnicowanych GEP-NEN (n = 57; 57%) rozpoznano w stopniu I klinicznego zaawansowania według klasyfikacji American Joint Committee on Cancer / Union for International Cancer Control (AJCC/UICC); 77% NEN G1 (n = 64) zdiagnozowano w stopniu I, jednakże większość nowotworów NEN G2 w stopniu IV (n = 18; 58%). U 38 pacjentów (34%) stwierdzono przerzuty w chwili rozpoznania. 90% nowotworów (n = 101) było nieczynnych hormonalnie. 5-letnia przeżywalność chorych wynosiła 85%. W analizach jednoczynnikowych czynnikami związanymi z gorszą prognozą były: stopień histologicznej dojrzałości NEN G2 (p = 0,003), wyższy stopień klinicznego zaawansowania według klasyfikacji AJCC/UICC (p <0,001) i obecność przerzutów w momencie rozpoznania (p <0,001). W standaryzowanych modelach wieloczynnikowych niezależnymi czynnikami ryzyka zgonu były wyższy stopień klinicznego zaawansowania (p = 0,02) i obecność przerzutów w chwili rozpoznania (p = 0,02).
WNIOSKI Najważniejszymi czynnikami wpływającymi na przeżywalność chorych z GEP-NEN są stopień klinicznego zaawansowania i obecność przerzutów w momencie rozpoznania. Analiza danych jednego ośrodka poprawia identyfikację pacjentów o gorszej prognozie, wymagających bardziej agresywnego postępowania.

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Supplementary material online

Fig. S1. GEP-NEN staging (AJCC/UICC 2009) according to tumor grade (WHO 2010) – for well-differentiated tumors, n=102.

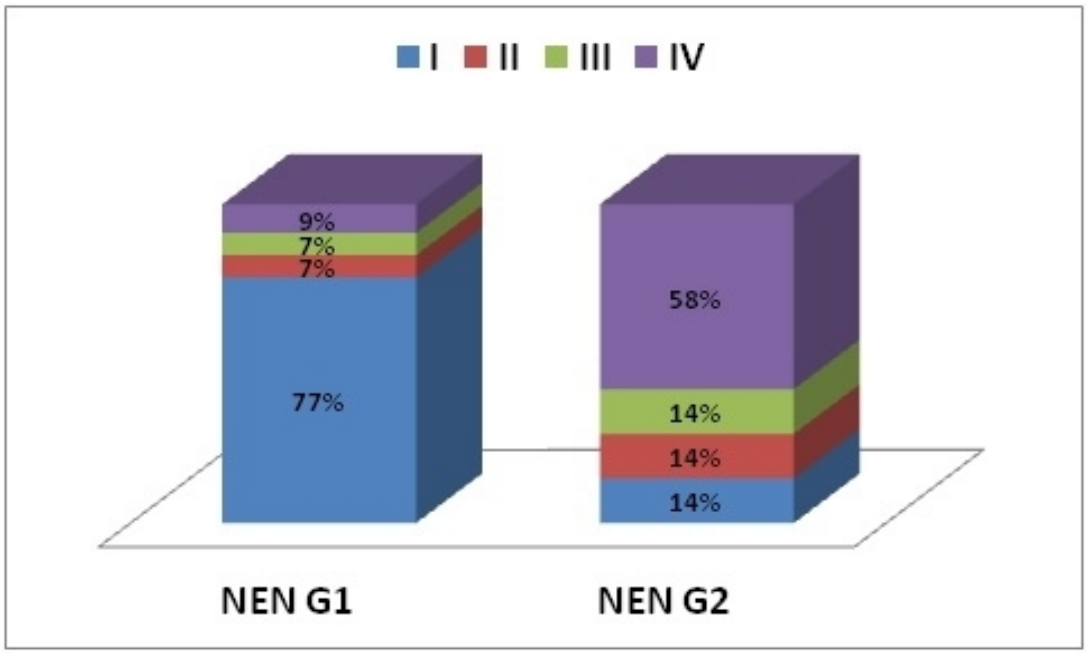

Fig. S2. Concurrent neoplasms according to GEP-NEN primary site (MN- malignant neoplasm, BN- benign neoplasm), n=121.

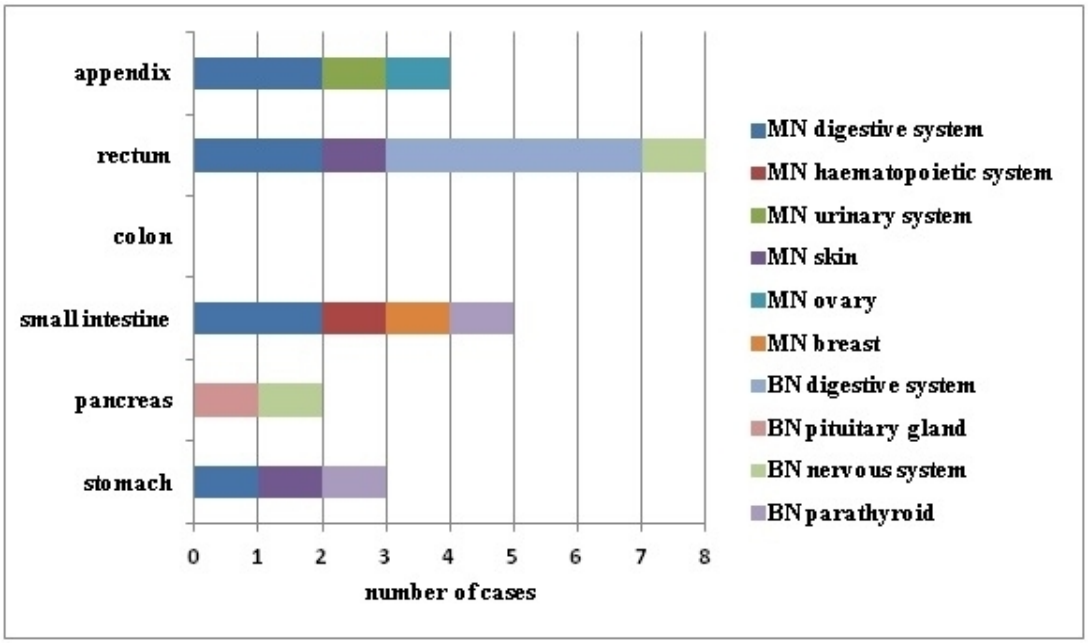

Fig. S3. Kaplan-Meier 5-year overall survival curves according to presence of metastases. Log-rank test for equality of survivor functions, $p<0.001$.