

## An epidemiological study of neuroendocrine tumours at tertiary hospitals in Bosnia and Herzegovina

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### ABSTRACT

**Aim** Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumours with varying clinical expression and behaviour. Because of indolent behaviour of NENs, reviewing and evaluation of epidemiological characteristics is a challenge. The aim of this study was to assess prevalence of NENs at tertiary hospitals considering age, gender, location, and grade.

**Methods** Electronic files were used for a retrospective assessment of the patients with NENs of the gastroenteropancreatic tract and bronchopulmonary system in tertiary hospitals in Bosnia and Herzegovina over the past 15 years (2005-2020).

**Results** Among 438 patients, 291(66.4%) were males and 147 (33.6%) females; the median age was 62 years. The lungs were the most frequent site, 304 (69.4%), followed by the pancreas, 22 (5.0%), colon, 14 (3.2%), stomach, 13 (2.9%), appendix, 13 (2.9%), rectum, 11 (2.5%), small intestine, eight (1.8%) and gallbladder, one (0.2%). Metastases were most frequently found in the liver, 35 (8%) and lymph nodes, 15 (3.42%).

**Conclusion** The results were largely consistent with those in literature, including age, gender, location, and the degree of differentiation. Most metastases originated from high-grade tumours and greater impairment of the liver.

**Key words:** epidemiology, incidence, neuroendocrine tumours, tertiary care centres

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## INTRODUCTION

Neuroendocrine neoplasm (NENs) is a heterogeneous group of tumours with differences in clinical expression and behaviour, ranging from relatively indolent to highly aggressive and fatal (1,2). These neoplasms originate from the cells of the diffuse neuroendocrine system distributed in many sites, amongst which most common are the gastrointestinal tract and pancreas, followed by the bronchopulmonary system (3). The NENs secrete peptides and neuroamines that may cause distinct symptoms termed “carcinoid syndromes”, in which case they are marked as “functional tumours” (4). The behaviour and aggressiveness of this neoplasm depend on a tumour size, secretion and histological grade of malignancy (5).

Unfortunately, because of their rarity, tumour heterogeneity and usually nonspecific presentation of symptoms, 40-50% of NENs patients have an advanced disease at the time of the diagnosis (6). Metastases may occur more frequently to the liver and are often presented by the time of primary diagnosis in 45-95% cases, causing shorter overall survival (7,8).

The diagnosis of a suspected neuroendocrine neoplasm requires a confirmation of neuroendocrine differentiation, using a panel of conventional neuroendocrine immunohistochemical markers such as chromogranin, synaptophysin, and CD56 (9). Mitotic counts and the Ki-67 protein-based cell proliferation index have become useful tools in assessing the malignant potential of NENs (5,10). Ki-67 proliferation marker had become an integral part of the World Health Organization (WHO) classification, as early as in the 2004 edition (11), as opposed to the lung NENs that mainly use a number of mitoses.

Epidemiological studies based on the US National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) cancer registry (12-14) and data from the National Cancer Registry of England for the period from 1971 to 2006, showed an increased global incidence of NENs in recent decades (15). It increases with age with a peak between 50 and 70 years of age.

The etiologic factors behind the increasing incidence and mortality for NENs are unclear (16,17). The improvement in the classification system, increased use of diagnostic techniques

(such as screening and diagnostic endoscopy), physicians’ awareness, and possible environmental factors (such as proton pump inhibitors) are considered responsible for the incidence increase (18,19).

In recent years, several useful and evidence-based classifications of NENs have been developed, differing between organ systems, and currently causing considerable confusion (20). In 2017, major changes in the grading and staging systems for pancreatic NENs were published: WHO grading systems changed the definition of grade 3 neuroendocrine tumours (NETs) to neuroendocrine carcinomas (NECs); the 8<sup>th</sup> American Joint Committee on Cancer (AJCC) changed its tumour-nodes-metastasis (TNM) based staging system for NEN; the treatment strategies changed according to the new concepts of grade 3 NET/NEC (21). In many organ systems NENs are graded based on mitotic count and/or Ki-67 labelling index, as well as the presence of necrosis (20). In the lungs, NENs are currently classified as low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AC), and the high-grade large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC) (10).

The aim of this study was to investigate epidemiological features of neuroendocrine tumours of the gastroenteropancreatic tract and the bronchopulmonary system of patients from hospital centres in Bosnia and Herzegovina (B&H) (gender, age, primary site, the existence or absence of metastases). This is the first multicentre study related to neuroendocrine neoplasms in Bosnia and Herzegovina.

## PATIENTS AND METHODS

### Patients and study design

Electronic files were used for a retrospective assessment of patients with the diagnosis of neuroendocrine neoplasm of the gastroenteropancreatic tract and bronchopulmonary system, from the Department of Pathology of the University Clinical Centre of Tuzla, University Clinical Centre of Sarajevo, East Sarajevo Hospital, General Hospital dr. Abdulah Nakaš (Sarajevo), Brčko District Hospital, and Cantonal Hospital dr. Irfan Ljubijankić (Bihać), over the last 15 years (2005 to 2020).

The data of the patients with neuroendocrine tumours were recorded and, based on pathology reports, analysed by gender, age, diagnosis, tumour location, primary site, and presence or absence of metastases. Patients without pathology reports were not included. No patients with mixed adeno-neuroendocrine tumours (MANETs) and carcinomas (MANECs) were found.

The study was approved by the Ethics Committee of the University Clinical Centre of Tuzla.

## Methods

Formalin fixed and paraffin embedded tissue blocks from biopsies and surgical materials were available for each patient. Hematoxylin and eosin stained slides were re-examined to confirm the original diagnosis. Conventional immunohistochemical markers of neuroendocrine differentiation (synaptophysin, chromogranin, CD56) were utilized to confirm the diagnosis. The Ki-67 immunohistochemical staining was performed on each specimen. Each neoplasm from the gastroenteropancreatic tract was classified according to the WHO classification 4<sup>th</sup> Edition for digestive system based on the mitotic count and Ki-67 index (5): G1 NETs - mitotic count of <2 per 10 high-power fields (HPF) and/or Ki-67 labelling index of ≤2%, G2 NETs- mitotic counts of 2 to 20 per 10 HPF and/or Ki-67 labelling index of 3% and 20% and NEC had mitotic counts of >20 per 10 HPF and/or Ki67 labelling index of >20%. Neuroendocrine tumour of the lung was classified according to the WHO classification 4<sup>th</sup> Edition (10).

## Statistical analysis

From the descriptive statistical parameters, absolute and percentage frequencies, and arithmetic means with corresponding standard deviations were calculated. From non-parametric statistical methods, the  $\chi^2$  test was applied, while from parametric statistical methods Student's t-test of independent samples was applied.

## RESULTS

A total of 438 patients with neuroendocrine (NEN) tumours of the gastroenteropancreatic tract and bronchopulmonary system was recorded in the period between October 2005 and February 2020: 304 (69.4%) were lung, 82 (18.7%) gastroenteropatic (GEP) and 52 (11.9%) metastatic NEN.

The number of patients increased over the years, with 185 in the period 2005-2014, and 251 in the period 2015-2020, resulting in the increase of 35.7%. Incidence showed an ascending trend from 2005 to 2016, from 0.03/100,000 to 1.61/100,000 per year, respectively, and with a drastic decrease in 2020, of 0.23/100,000 (Table1).

**Table 1. Incidence of neuroendocrine neoplasm (NEN) in Bosnia and Herzegovina (B&H) in the period October 2005 - February 2020**

Year	Number of patients	B&H population	Incidence per 100,000
2005	1	3842527*	0.03
2006	3	3842762*	0.08
2007	9	3842562*	0.23
2008	12	3842265*	0.31
2009	19	3842566*	0.49
2010	23	3843126*	0.60
2011	16	3843000*	0.42
2012	22	3839737*	0.57
2013	42	3531159†	1.19
2014	40	3531159†	1.13
2015	50	3531159†	1.42
2016	57	3531159†	1.61
2017	43	3531159†	1.22
2018	49	3531159†	1.39
2019	44	3531159†	1.25
2020	8	3531159†	0.23
<b>Total</b>	<b>438</b>		

\*Population estimate – Agency for Statistics of B&H; †Population Census in B&H (2013) – Agency for Statistics of B&H

Of 438 patients, 291 (66.4%) were males and 147 (33.6%) were females. The median age was 62 years (range 17-85). The mean age was 61.28 years; males were older compared to women, 61.90±1.24 and 60.05±1.92 years, respectively ( $p < 0.101$ ). The most frequent age group was >60 years, 258 (59.2%), 158 (36.2%) were between 40-60 years, and 20 (4.6%) were below 40 years of age.

Among 304 lung NENs, small cell lung carcinoma was mostly presented, in 271 (89.1%) patients (Table2).

**Table 2. Characteristics of different histological types of lung neuroendocrine neoplasms**

Histological type	Number (%) of patients	Mean age (years)	Male/Female ratio
SCLC	271 (89.1)	62.2	2.9
LCNEC	19 (6.25)	63.9	2.8
AC	8 (2.63)	59.9	1.7
TC	6 (1.97)	54.0	0.5
<b>Total</b>	<b>304 (100)</b>	<b>60.0</b>	<b>2.7</b>

SCLC, small cell lung carcinoma; LCNEC, large cell neuroendocrine carcinoma; AC, atypical carcinoid, TC, typical carcinoma

In eight (15.4%) patients with small cell carcinoma, biopsy was obtained from the metastases, which were most frequently found in the liver, lymph nodes, and brain.

NENs of the gastroenteropancreatic tract were found in 82 (18.72%) patients. According to the anatomical site, pancreas was most frequent, 22 (26.8%), followed by the colon, 14 (17.1%), stomach, 13 (15.8%), cecal appendix, 13 (15.8%), rectum, 11 (13.4%), small intestine, eight (9.7%) and gallbladder in one (1.2%) patient. Tumours originating from the colon and stomach were mostly poorly differentiated, 11 (33.3% and 9 (27.3%), respectively. NET G2 was most frequent in the pancreas, 12 (60%), and NET G1 in cecal appendix, 10 (34.5%) (Table 3).

**Table 3. Characteristics of gastroenteropancreatic neuroendocrine neoplasms according to the site and grade**

Characteristic	Number (%) of patients			Total
	G1	G2	NEC	
Anatomical site				
Pancreas	6 (27.3)	12 (54.5)	4 (18.2)	22
Colon	3 (21.4)		11 (78.6)	14
Stomach	1 (7.7)	3 (23.1)	9 (69.2)	13
Cecal appendix	10 (76.9)	3 (23.1)		13
Rectum	5 (45.5)		6 (54.5)	11
Small intestine	4 (50)	2 (25)	2 (25)	8
Gallbladder			1(100)	1
Mean age (years)	53.90	53.10	64.42	57.94
Male/ Female ratio	1.23	0.82	1.36	1.16
<b>Total</b>	<b>29</b>	<b>20</b>	<b>33</b>	<b>82</b>

G1, grade 1; G2, grade 2; NEC, neuroendocrine carcinoma

Among 52 metastatic NENs, 44 (84.6%) of the gastroenteropancreatic tract were detected, the most frequently in the liver and lymph nodes. Of 35 (79.5%) cases in the liver, NEC was most frequent, with 21 (60%) cases, followed by 9 (25.71%) cases of NET G2 and five (14.28%) cases of NET G1. Lymph nodes accounted to 9 (20.5%) cases of metastatic neuroendocrine tumour of the gastroenteropancreatic tract (data not shown). The vast majority of metastatic cases was neuroendocrine carcinoma but some cases were classified as NET G1 and NET G2 presented with metastases even when they had a low proliferative index.

Regarding the age and grades of NENs, NET G1 and NET G2 frequently appeared below 40 years of age, while SCLC, LCNEC, and NEC of the gastroenteropancreatic tract were most frequent after 60 years of age. Metastatic NENs in the liver and lymph nodes were found mostly in the patients above 60 years of age.

**DISCUSSION**

In this study epidemiological features of neuroendocrine tumours of the gastroenteropancreatic

tract and bronchopulmonary system from hospitals in Bosnia and Herzegovina were described. This is the first multicentre study which included the distribution of neuroendocrine tumours from a tertiary hospital database over the last 15 years. A limiting factor of this study was the lack of complete data, but considering the fact that in Bosnia and Herzegovina there is no register for this type of neoplasm, our study is very important.

Based on the current medical literature, the overall incidence of NENs is rising (3). The SEER (Surveillance, Epidemiology, and End Results) database and national cancer registries in Western Europe are probably some of the most publicly available cancer registries (22). Our study showed a significant increase in the number of cases (of 35.7 %) for the period between 2015 and 2020, compared with the period 2005-2014, mainly due to a greater access to complementary diagnostic tests, such as imaging technique, endoscopic procedures and histopathology examination of these tumours. Accordingly, an increase in incidence was also noticed, from 0.03 in 2005 to 1.61 in 2016, which is consistent with SEER database showing incidence steadily increasing over the past four decades (from 4.2 in 1993-1997 to 5.8 in 2000-2004) (13).

The incidence of NENs increases with age, and it peaks between the sixth and the seventh decade. In the gastrointestinal tract, the median age is less than 50 years of age, for appendix and pancreatic NENs, and more than 60 for other organs (23). In the bronchopulmonary system contrary to small cell lung carcinoma, the lung carcinoid occurs in younger and non-smoker patients (10) and can be cured with surgical excision. The mean age (61.28 years) in our study was similar to a study from Norway (61.5 years) (24), but slightly higher compared to studies in France, China, Germany and Spain (56 years) (25-28).

There are some minor differences relating to the gender and race, between the countries/continents, and in some cases the changes over time have been noticed (22). Our study showed a male predominance, which was consistent with results of Norway, France, China, Germany and Spain studies (24-28).

Neuroendocrine tumours are commonly found in the gastrointestinal tract, pancreas and the lung but it is not unusual to find neuroendocrine tu-



mours in the thyroid, skin, breast and other organs (29-31). Consistent with the Kentucky Cancer Registry (KCR) and SEER, between 1995 and 2015 (30.6%) (32), as well as a nation-wide study from the Netherlands (72.7%) (23), the most common NEN sites in our study was the lungs (69.4%). The distribution of the types of lung neuroendocrine tumours was similar to that in the literature, with small-cell carcinomas being the most frequent tumour (33,34).

Regarding the most frequent primary site in the gastroenteropancreatic tract, our data was consistent with studies from Germany, Italy, Lebanon, Spain and Mexico (35-39), with the pancreas being the most frequently affected organ. Although the small intestines are currently in some parts of Europe the most common primary sites for NENs of the gastroenteropancreatic tract (24,25,40), the highest increase in prevalence rate in recent years has been observed for gastric and rectal NENs, which is consistent with our data. The widespread usage of proton-pump inhibitors has been proposed as a possible risk factor for the highest increase of gastric NENs (41). Appendix NEN was more frequent among Western countries (16.7%), which could be explained by accidental findings on appendectomy performed for acute appendicitis (42). Rectal NEN was the most common site in Asian populations (30.6%) (43). Our study showed 15.85% cases of appendix and 9.76% of small intestine NEN.

Prevalence of NENs of the gastroenteropancreatic tract in our population is consistent with

the data in the literature (23,43); G2 pancreatic NENs were most frequently encountered, which is consistent with a study from Germany (35). G1 and G2 were the most frequent grades among cecal appendix tumours (none of which presented with metastases), and NET G1 among tumours of the small intestine, which also consistent with findings reported in the literature (44).

In conclusion, to our knowledge this is the first multicentre study of NENs epidemiology in Bosnia and Herzegovina. Compared with the results of other studies, our results were largely consistent with those in the literature, especially regarding the age group, gender, and location. Because of the heterogeneous nature of these tumours that vary in origin, morphology, molecular profile, type and site-specific prognosis, aggressiveness and response to therapy, the management of these tumours requires a multidisciplinary approach. Future studies to clarify etiologic factors are needed.

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#### TRANSPARENCY DECLARATION

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