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# Neuroendocrine tumor of the pancreas - our experience with resectable tumor

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**Abstract** Pancreatic neuroendocrine tumors are still rare, but their incidence is increasing. They form a heterogeneous group of tumors with rapid growth and metastatic progression. This article aims to share basic information about pancreatic neuroendocrine tumors and to share information about the incidence in our cohort of patients after pancreatic resection procedures.
**Keywords** pancreas, NET, resection, surgery, risk factors

## 1. INTRODUCTION

Neuroendocrine tumors (NET) originate in the cells of the diffuse neuroendocrine system from the islet cells of the pancreas. They form an extremely heterogeneous subgroup, both taking into account the histological endocrine characteristics, as well as the clinical manifestations of the disease, and, last but not least, the rapid tendency to form metastases. According to the latest scientific information, pancreatic NET has a rising incidence and accounts for up to 2-4 % of pancreatic tumors (1-4). Since they originate from the cells of the neuroendocrine system, they can secrete hormonally active substances. According to the production of a specific amine (peptide), we also call them gastrinomas, insulinomas, VIPomas, somatostatinomas, etc. However, most of them are neuroendocrine dysfunctional. Compared to ductal adenocarcinoma of the pancreas, up to 64 % of patients have metastatic liver damage when the tumor is detected (5). Approximately 57 % of patients survive less than five years (4,6). Diagnosis NET of the pancreas is still challenging. Definitive confirmation of the diagnosis is based on histological typing, staging, and grading of the disease and biological mechanism. Computed tomography (CT) is the primary imaging method due to the diagnostic workload, availability, and reproducibility. If treatment monitoring is performed mainly by CT, a three-phase CT should be performed (7). Magnetic resonance imaging (MRI) is preferred for initial staging. Its sensitivity is approximately 79 % for NETs of the liver and pancreas (8). An imaging method with the possibility of biopsy is endoscopic ultrasonography, which shows the anatomical localization and staging of the tumor (9). The treatment of these tumors is based on resection. For resectable pancreas tumors, we perform pylorus-preserving pancreatoduodenectomy or distal hemipancreatectomy; it depends on anatomical localization. We will continue to focus on resectable pancreatic tumors in our cohort of patients. There is also hope for patients with metastatic liver damage, where surgical management is recommended according to the latest scientific information.

## 2. MATERIAL AND METHODS

We retrospectively monitored pancreatic resection procedures at the I. department of surgery of UPJŠ and UNLP in Košice. Between January 1, 2018, and July 31, 2023, we monitored hospitalized patients who underwent pancreatic resection surgery. A total of 132 patients underwent pancreatic resection surgery during this period due to oncological disease. We focused on the occurrence of

individual histological types of pancreatic tumors, the type of resection procedure, and the relationship with gender and age. All patients were over 18 years of age and signed informed consent. The analyzed sample consisted of 132 patients over five years. The patients had a pre-operative preparation, the basis of which was a CT imaging examination of the abdomen (figure 1, figure 2). Subsequently, they were operated on, and the tissue was sent to the Department of Pathology of UNLP and UPJŠ in Košice for histological examination. Later, they were monitored postoperatively and discharged to home care when informed about the histological examination results and further treatment management. We divided the patients into categories based on the TNM classification. We present the TNM classification in Table 1.

Table 1: Definition of American Joint Committee on Cancer (AJCC) and European Neuroendocrine Tumor Society staging for pancreatic neuroendocrine tumors

| **AJCC 8th and ENETS staging classification** | |
|---|---|
| **T1** | Tumor limited to the pancreas ≤ 2cm |
| **T2** | Tumor limited to the pancreas 2-4 cm |
| **T3** | Tumor limited to the pancreas > 4 cm or invading the duodenum or common bile duct |
| **T4** | Tumor invades adjacent structures |
| **N0** | No regional lymph node metastasis |
| **N1** | Regional lymph node metastasis |
| **M0** | No distant mestastasis |
| **M1** | Distant metastasis |
| **M1a** | Metastasis confined to the liver |
| **M1b** | Metastasis in at least one extrahepatic site |
| **M1c** | Both hepatic and extrahepatic metastases |

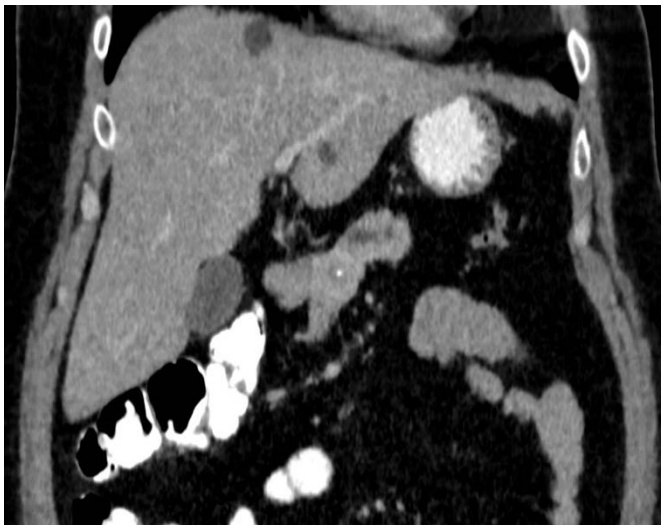


Figure 1: Transverse CT section of the abdomen showing a pancreatic body tumor with calcification

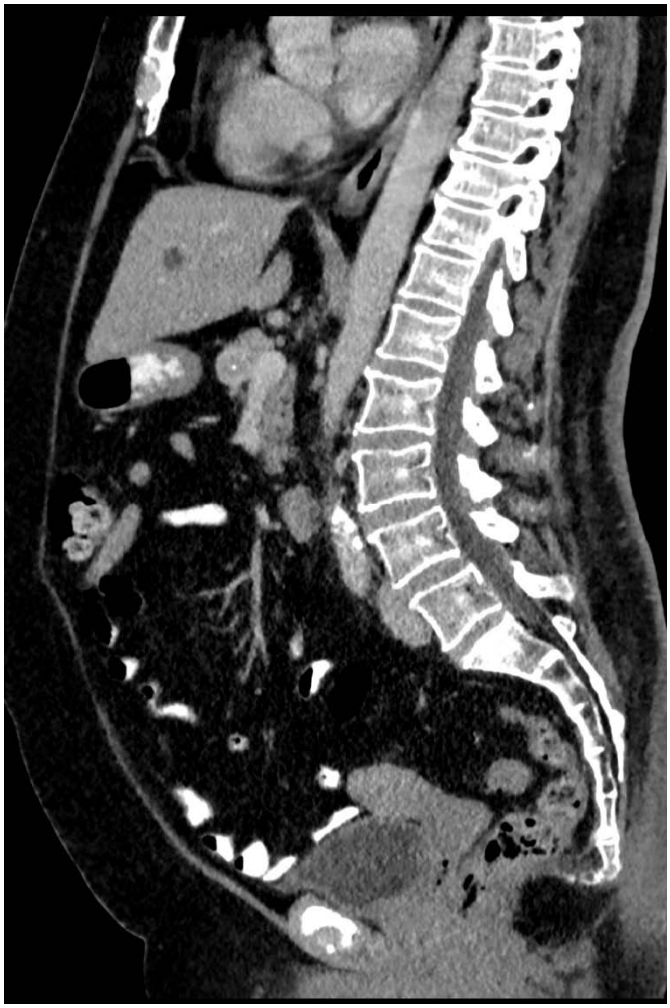


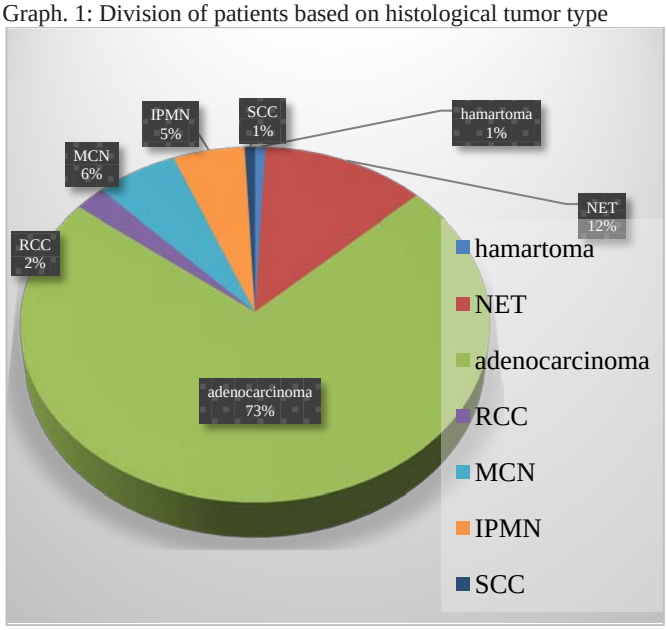
Figure 2: Sagittal CT section of the abdomen showing a pancreatic body tumor with calcification

## 3. RESULTS

One hundred thirty-two pancreatic resection procedures were performed at I. department of surgery, UPJŠ, and UNLP Košice. We divided them into groups according to histological type. The largest group consisted of patients with adenosquamous carcinoma, 96 patients, i.e., 72,73 %. Up to 16 patients were diagnosed with NET, i.e. 12.12 %. Invasive mucinous cystic neoplasm (MCN) comprised 6,06 %, i.e., eight patients. Invasive intraductal papillary mucinous (IPMN) made up 5,30 %, i.e. seven patients. Metastasis of renal cell carcinoma (RCC) included three patients, i.e., 2,27 %. Harmatoma, 0,76 %, and squamous cell carcinoma (SCC), 0,76 %, were in last place after one patient. You can see the histological representation on the graph.1. Since we were surprised by the histological representation of NET in the second place, we decided to deal with it. The average age of patients with pancreatic NET was 64 years (range 27-78 years). Our research sample comprised nine men (56 %) and seven women (44 %). We decided to compare the occurrence of NET and adenocarcinoma since this is the most represented type of tumor concerning gender. We aimed to calculate the odds ratio to the type of cancer between adenocarcinoma and NET. The chance that a patient from our research group will get NET is 0,17. The odds ratio for NET and male gender, among the non-influential risk factors, is 0,86. The odds ratio for adenocarcinoma and male gender is 1,041. We also focused on the increasing incidence of patients with NET for the year. In the first years (2018 and 2019), we recorded only one patient yearly. The

outbreak began in the rest of 2020 when two patients occurred. In 2021, we had five patients. In 2022, we had four patients; so far 2023, we have recorded three patients. According to our patient database, the survival of patients with NET is, on average, 44 months (2 to 58 months), while the survival of adenocarcinoma is only 38 months (0 to 58 months). Based on tumor localization and preoperative CT staging, surgical techniques were selected. If the tumor was located in the head or body of the pancreas, we performed a pylorus-preserving pancreatoduodenectomy. We achieved this surgical procedure in 10 patients, i.e., 62,5 %. When the tumor was located in the tail of the pancreas, we performed a distal hemipancreatectomy. We achieved this surgical procedure in 6 patients, i.e., 37,5 %.

Graph. 1: Division of patients based on histological tumor type




## 4. DISCUSSION

Our main goal of the work was to focus on individual histological subtypes of pancreatic cancer. We were surprised that NET came in second place in terms of occurrence. We decided to pay attention to the localization of the tumor, risk factors, and rising incidence of NET. We confirmed the correlation that NETs affect younger patients and have better survival than adenocarcinomas. Siddharta also confirmed this relationship in 2018 and evaluated the results from 57,688 patients using a meta-analysis (10). NETs are often associated with germ-line mutation causing multiple hereditary endocrinopathies, such as multiple endocrine neoplasia type I or type IV, von Hippel-Lindau disease, and neurofibromatosis type I (11). However, we did not focus on this genetic correlation in patients within our database. Since it would be necessary to carry out genetic tests, not only a standard histological examination. NETs have a specific clinical sign due to excessive secretion of tumor hormones, such as excess insulin (insulinoma), gastrin (gastrinoma), glucagon (glucagonoma), vasoactive intestinal peptide (VIPoma), somatostatin (somatostatinoma) or pancreatic polypeptide (PPoma) (12). In up to 60 % of cases, however, they may be non-functional (13). We performed a retrospective analysis based on medical records. Unfortunately, we do not know the clinical symptoms of our patients before diagnosing the disease. Since, as mentioned before, the incidence of NETs continues to rise, new diagnostics for these tumors are also coming to the fore. Currently, CT imaging examinations of the abdomen are the basis of diagnosis due to the staging of the disease. If NET is suspected, more than galium-68 positron emission tomography or fluorodeoxyglucose positron emission tomography should be performed (14, 15). However, the research focuses on the detection of new pancreatic NET markers, e.g., of circulating tumor cells, test (PCR-based test for detection NET), and determination of cytokinins, which play a role in the pathogenesis of the disease (16-18). After determining grading and staging, the surgeon decides on the type of surgical procedure. Based on workplace standards, preserving pylorus pancreatoduodenotomy or distal hemipancreatectomy is performed based on anatomical location. These two surgical procedures are among the worldwide standards of treatment (19). In some cases, however, according to the latest guidelines, enucleation is recommended (20). According to available scientific information, enucleation is recommended for tumors smaller than 2 cm (21). In larger tumors, local lymph nodes are always affected, so radical dissection is necessary. However, the question of monitoring tumors smaller than 2 cm remains open. Several studies have shown a clear correlation between tumor size and a lower potential for malignancy, so this observation is acceptable for patients with NETs smaller than 2 cm (22,23). The postoperative follow-up of the patient is essential. The standard is postoperative checks every three months, which include USG of the abdomen, a basic biochemical blood test supplemented with oncomarkers. Every year, during the first three years, a control CT or MRI of the abdomen should be performed (24). However, the increasing incidence of NET remains an open question. Different population studies have shown an increase in NET incidence (25,26,27). Some studies attribute the growing incidence of the increased incidence of pancreatic cancer to better diagnosis of the initial stages of the disease. Specific preoperative tests and imaging methods also contribute to the increased rate of NET diagnosis (28). There is no substantiated evidence, but the rising incidence may be related to lifestyle (stress, obesity, smoking, alcohol abuse). In terms of uncontrollable risk factors, the association between NET and pancreatic cancer and the male gender was confirmed (29).

## 5. CONCLUSION

NETs are among the rare tumors of pancreatic cancer but with increasing incidence. Our retrospective study focused on the representation of histological subtypes in patients after pancreatic resection procedures. Within the framework of risk factors, a statistically significant connection between the male gender was confirmed. When comparing patients with adenocarcinoma and NET, we ensured better survival in patients with NET. The increased incidence of NET may be associated with better diagnostics, more specific methods for NET detection, and lifestyle.

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