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Increased prevalence of pancreatic neuroendocrine microadenomas in patients with intraductal papillary mucinous neoplasms: yet another example of exocrine-neuroendocrine interaction?

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Abstract

Introduction. Intraductal papillary mucinous neoplasms (IPMN) and neuroendocrine tumors (NET) may develop simultaneously in the pancreas. Neuroendocrine microadenomas (NMA) are precursor lesions for NET. The study aimed to determine the prevalence of NMA/NET in patients with IPMN in a series of resection specimens.

Material and methods. Some 232 prospectively gathered specimens were included and examined histopathologically: 51 IPMN, 114 conventional pancreatic ductal carcinomas (PDAC) and 67 ampullary carcinomas (AMPCA).

Results. NET were rare in the study samples (single cases among IPMN and AMPCA, and two cases among PDAC). In contrast, NMA were frequently found in IPMN specimens when compared to samples of PDAC and AMPCA (27.45%; 7.89%, and 7.46%, respectively, $p < 0.001$). Two NMA in IPMN group were related to ducts, but no case of composite (clonal) IPMN/NMA was found.

Conclusions. IPMN specimens were enriched in NMA but not in NET. IPMN/NMA association may serve as a model of exocrine-neuroendocrine interaction.

Key words: pathology, pancreas, pancreatic neoplasms, pancreatic intraductal neoplasms, islet cell adenoma

Introduction

Intraductal papillary mucinous neoplasms (IPMN) are macroscopically detectable epithelial proliferations within the pancreatic ductal system, which may progress to invasive ductal carcinomas. Neuroendocrine tumors (NET) of the pancreas are usually slow-growing neoplasms, which are sometimes associated with symptoms of hormone secretion sydromes. Neuroendocrine microadenomas (NMA) are defined as pancreatic non-functioning neuroedocrine neoplasms of less than 5 mm in diameter. NMA are considered precursor lesions for NET [1].

Some investigators hypothesized that pancreatic NET may preferentially develop in patients with IPMN (or *vice versa*), so IPMN and NET may be found simultaneously in the pancreata at higher rate than expected. This suggested that IPMN/NET coexistence could be not necessarily accidental [2]. However, literature data on IPMN/NET association are limited [2–15].

Importantly, IPMN and NET may coexist as independent tumors within pancreas separated by parenchymal tissue or they may form a single lesion [4]. The latter usually develops as a collision tumor, i.e. it consists of topographically related components of most likely independent origin without shared molecular alterations [14]. Recently, several investigators showed that IPMN and NET components within a single IPMN/NET mass may in fact share molecular profile [13, 14]. This observation served as a proof on a common origin of both components in some very rare IPMN/NET cases (so-called composite tumors) [13, 14]. Management of patients with IPMN/NET is not well established. Possibly they should be managed as it is indicated by the nature of each tumor component separately [7].

The purpose of the study was to determine the prevalence of NMA/NET in patients with IPMN in a large single-center histopathological series of pancreatic resection specimens. For comparative purposes, specimens of patients with conventional pancreatic ductal carcinomas (PDAC) as well as ampullary carcinomas (AMPCA) were taken. The study was designed aiming to exhibit whether IPMN may favour development of NMA/NET within pancreas. Additionally, the study focused on microscopical appearance of IPMN/NET lesions/components in the context of potential relatedness of both entities.

Material and methods

Histopathological data on nearly consecutive in-house cases of IPMN of the pancreas diagnosed in resection specimens in the author's insititution between July 2015 and March 2021 were retrieved from a prospective database of pancreatic resection samples. Samples of conventional PDAC (i.e. not derived from IPMN) diagnosed between January 2017 and March 2021 as well as samples of AMPCA diagnosed between July 2015 and March 2021 were taken for comparative purposes. Cases were qualified into particular study groups based on histopathological diagnosis of primary lesion, i.e. a mass which was the main indication for surgery [3].

A small number of cases encountered in study period were excluded from the study for several reasons (eg. specimens obtained following neoadjuvant therapy, rare specimens examined using only representative tissue sections due to technical/billing reasons, enucleation/limited resection specimens, specimens obtained in palliative resections, rare cases dissected by other pathologists).

Importantly, the present study was based on standardized histopathological examination of surgical specimens. All included cases were macroscopically and microscopically examined by a dedicated pathologist (this author) in a standardized fashion, i.e. entire resected pancreatic tissue was taken for microscopical examination irrespective of its gross appearance. Pancreaticoduodenectomy specimens were processed using Leeds Pathology Protocol.

Histopathological diagnoses were established based on the WHO 2019 criteria [1]. Diagnoses established before 2019 were re-assessed for the purpose of the study. In particular, NMA was defined as a clinically-silent neuroendocrine proliferation less than 5 mm in diameter, and additionally:

- demarcated from pancreatic parenchyma by fibrous (pseudo)capsule, and/or
- having trabecular/solid architecture, and/or
- showing abundant stroma, and/or
- presenting with altered distribution of pancreatic hormones in immunohistochemical (IHC) studies [1].

Effort was made to distinguish NMA from its mimickers: islet aggregations and (pseudo)hyperplasia. In brief, islet agreggations are typically found in severely atrophic parenchyma, do not show expansive growth and/or trabecular tissue composition, and usually retain topographical distribution of expression of pancreatic hormones (albeit increase of glucagon-producing cells and reduction of insulin-producing cells are allowed). Islet hyperplasia is a diffuse enlargement of islets (with ot without cytological alterations in endocrine cells), which usually involves entire pancreas and frequently results in clinical symptoms. Size, shapes as well as hormone distibution patterns of pancreatic islets in hyperplasia are altered. Islet pseudohyperplasia involves typically uncinate process and it is asymtomatic. In selected cases hormone immunostains were helpful for differential diagnosis of NMA. Lack of expression or overexpression of a particular hormone, or abnormal distribution of pancreatic hormones within a lesion favoured NMA over reactive endocrine proliferations [15–17].

For comparison of continuous variables, Kruskal-Wallis ANOVA or Mann-Whitney U tests were used, as appropriate. Ordinal/nominal variables were compared using Chi2 tests. Statistical significance was set up at $p \leq 0.05$.

Institutional Review Board permitted to perform the present observational study without full review, which is necessary for interventional studies on humans, according to national regulations.

Results

Study groups

Some 232 resection specimens were included in the study: 51 cases of IPMN (with or without coexistent invasive carcinomas), 114 cases of PDAC and 67 cases of AMPCA. Invasive adenocarcinomas were found in 51% samples with IPMN. Gastric and intestinal IPMN subtypes were most prevalent. Most invasive carcinomas associated with IPMN (58%), as well as most PDAC (91%), and AMPCA (91%) were conventional tubular adenocarcinomas, as expected. All but one invasive cancers coexistent with IPMN were interpreted as derived from IPMN, a single sample was considered equivocal (i.e. it was not clear if invasive cancer was related pathogenetically to IPMN, as described below). Invasive cancers associated with IPMN as well as AMPCA were significantly smaller than conventional PDAC (median 17 mm *vs*. 15 mm *vs*. 31.5 mm, respectively, $p < 0.001$). Not surprisingly, primary tumour stage and frequency of metastases in regional

lymph nodes were lower in carcinomas derived from IPMN in comparison to PDAC. IPMN-related cancers were also enriched in G1 tumours.

There were also some differences related to types of specimens examined within study groups: the majority of conventional PDAC were found in pancreaticoduodenectomy specimens, and total pancreatectomies were performed mainly due to IPMN, as expected. Importantly, median numbers of tissue blocks examined per specimen were similar across the study groups ($p = 0.199$). Details on demographical and histopathological characteristics of study populations were described in table I.

NMA/NET in the study groups

A single case of NET was found in IPMN group (prevalence of 1.96%). This was a 7-mm incidentally detected, non-functional, and presumably sporadic G1 tumour in 61-year old man treated with total pancreatectomy due to diffuse low-grade gastric mixed-duct type IPMN of the pancreatic head (formerly IPMN with moderate grade dysplasia). Additionally, 3-mm focus of invasive G1 adenocarcinoma in close association with non-dilated duct of the pancreatic tail with high-grade pancreatic intraepithelial neoplasia was found. It was not clear if invasive cancer was pathogenetically related to IPMN, as dysplastic lesions of various grades were found in many dilated/non-dilated ducts within pancreas. NET was seen in pancreatic head and it was composed of trabeculae in sclerotic stroma. NET extended focally to the peripancreatic adipose tissue, but perineural/vascular invasion was absent. NET was not associated topographically with IPMN (not shown). Additionally, three IPMN-independent NMA were found in the pancreatic head.

Two NET cases and a single NET case were found in patients with PDAC (2/114; 1.75%) and AMPCA (1/67; 1.49%), respectively. The frequencies of NET did not differ across all three study groups (IPMN *vs.* PDAC *vs.* AMPCA; $p = 0.981$).

These numbers contrasted with prevalence of NMA, which were found in larger proportion of IPMN cases (14/51; 27.45%), in comparison to PDAC cases (9/114; 7.89%) and AMPCA cases (5/67; 7.46%). That difference was statistically significant ($p < 0.001$) and odds ratio for NMA in IPMN *versus* NMA in PDAC was 4.41 (95% CI; 1.61–12.49), whereas odds ratio for NMA in IPMN *versus* NMA in AMPCA was 3.85 (95% CI; 1.24–13.17).

Enrichment of IPMN group in NMA resulted also in larger proportion of NMA/NET counted in aggregate in specimens with IPMN (27.45%) in comparison to PDAC (8.77%) and AMPCA samples (8.96%, $p = 0.002$). Frequencies of NMA/NET across the study populations were summarized in table II.

IPMN with and without coexisting NMA/NET

Patients treated with pancreatic resections due to IPMN with and withour NMA/NET (i.e. in essence: with/without NMA) did not differ in terms of their age and sex. Interestingly, NMA/NET in IPMN group were somewhat frequent in distal pancreatecomy samples (5/16) and total pancreatecomy samples (8/19) in comparison to pancreaticoduodenectomy specimens (1/14 samples), but that difference did not reach

statistical significance (p=0.086). Coexistent NMA/NET was a rare finding when IPMN was localized in the pancreatic head (1/22), but frequent one when IPMN diffusely involved the entire pancreas (8/12) ($p < 0.001$). Histological type of IPMN, grade of dysplasia, or presence of invasive cancer did not affect the prevalence of NET/NMA in patients with IPMN. However, NMA/NET were more likely to be found in IPMN samples with limited invasion ($p = 0.007$). The prevalence of NMA/NET in IPMN samples was not biased by volume of resected pancreatic tissue ($p = 0.527$). Histopatological characteristics of IPMN with and without NMA/NET were compared in table III.

NMA in the IPMN group – histopathological characteristics

NMA were found in 14 specimens showing all grades and histological types of IPMN. The number of NMA per specimen ranged from 1 to 6 (median 1). Diameter of NMA ranged from 0.5 mm to 3.8 mm. In 8/14 cases NMA were found in distal pancreas, in 5/14 – in pancreatic head, in a single case NMA were found in both segments of the pancreas. NMA were localized within atrophic lobules in a half of IPMN samples. Direct connection of NMA and ducts was found in only two NMA across all the 14 IPMN samples with NMA:

- in a single case (sample no. 10) 3.8 mm NMA did not have connection with IPMN (fig. 1A), but encircled a small duct and showed partial intraductal spread (fig. 1B). The lesion was synaptophysin-positive (fig. 1C and fig. 1D), chromogranin-A-positive (not shown), but did not express serotonin (not shown). Ki-67 was weakly positive in just several tumour cells (not shown),
- in another case (sample no. 13) 2.5 mm NMA was localized in atrophic lobule surrounded by IPMN lesion (fig. 2A and 2B). NMA was chromogranin-A-positive (not shown), synaptophysin-positive (not shown), glucagon-positive (fig. 2C), and insulin-negative (fig. 2D). Ki-67 proliferative index was 1% (not shown).

Other NMA did not develop within IPMN (as reported previously in composite IPMN/NET tumors [13, 14]), and did not have direct connection with ductal epithelium. Representative examples of some NMA are depicted in fig. 3. Histopathological details of NMA/NET in samples with IPMN are presented in table IV.

Type of resection specimens as a potential confounding factor

As described above, NMA/NET in IPMN specimens were found mainly in distal pancreatectomy and total pancreatectomy samples rather than in pancreaticoduodenectomy samples. This may suggest a systematic bias, as distal pancreas was infrequently resected in patients with PDAC/AMPCA (tab. I). However, distal pancreatectomy specimens with IPMN were enriched in NMA (5/16; 31.25%) in comparison to distal pancreatectomy specimens with PDAC (3/30; 10%). The difference was not significant ($p = 0.070$), possibly due to limited number of distal pancreatectomy samples. Prevalence of NMA/NET in pancreaticoduodenectomy specimens did not differ accross three study groups ($p = 0.964$).

Discussion

The present study has shown that pancreata with IPMN may be enriched in neuroendocrine neoplasms. In particular, NMA were found in 27% of IPMN specimens. Majority of NMA were found in distal pancreas, and distal pancreatectomies performed due to IPMN were specifically enriched in NMA in comparison with PDAC specimens. However, NMA in IPMN specimens were usually solitary lesions. Microadenomatosis (i.e. multiple, usually uncountable NMA [1]) was not found in any case. No case showed histopathological picture suggestive of composite IPMN/NET(NMA), as NMA/NET tissue was not in direct contact with IPMN.

NMA/NET prevalence

The results of the study should be interpreted in the context of „baseline" prevalence of NMA/NET in the population. The real incidence of NMA/NET is diffucult to estimate, as only a fraction of them come into clinical attention due to symptoms or as asymptomatic "incidentalomas" found during diagnostic/radiologic work-up performed for other reasons. Incidence of clinically-detected pancreatic NET has increased substantially during the last decades [18], but it is still below rates based on autopsy studies [16]. In their autopsy study Kimura et al. found NMA/NET in 6/60 (10%) totally embedded pancreata and in 12/738 (1.6%) pancreata examined by representative tissue sections [16]. In other autopsy studies frequency of pancreatic NET ranged from 0 to 1.4% (as reviewed in [16] and [19]). The prevalence of NMA/NET in retrospective clinical-histopathological studies ranged from 1.4% [15] to 4% [3].

In the present study the prevalence of NMA/NET in the „control" groups (i.e. PDAC and AMPCA) was between 7 and 9%. These numbers were close to the autopsy-based results in totally embedded pancreata (10%) [16]. Therefore it may be assumed that the baseline frequency of NET/NMA under chosen diagnostic approach is probably somewhere around 7-10%. It should be empasized that the majority of NMA/NET are self-limiting lesions of little clinical significance [3]. However, some rare NMA may have potential of malignant behaviour [15]. In 2023 WHO classification NMA will be renamed as neuroendocrine microtumors as they may very rarely metastasize to the lymph node [20].

It should be also kept in mind that the prevalence of NMA in surgical specimens is strongly related to numerous laboratory factors:

- volume of pancreatic tissue available for analysis,
- extensiveness of tissue sampling for histology,
- thickness of tissue sections,
- careful exclusion of NMA mimickers, and
- diligence during microscopical examination.

NMA/NET in patients with IPMN

NMA/NET coexisting with IPMN are rare, with less than 50 reported cases [7]. At the moment it is not fully clear whether IPMN and NMA/NET coexist more frequently that expected. and whether there is causal relationship between IPMN and NMA/NET [2, 4]. The only exception are recent reports which proved that both IPMN and NET components within a single composite IPMN/NET lesion may be clonally related [13,

14]. In contrary, other investigators did not found evident molecular relationship between topographically related IPMN and NET [5]. These observations indicate that clonally related IPMN/NET is possible, but exceedingly rare lesion.

Results of previous studies on IPMN/NET association gave discrepant results. Sahora et al. noticed that prevalence of NET in patients with IPMN is similar to the general population and frequency of NET in specimens with IPMN is similar to the frequencies of other incidental pancreatic neoplasms [8]. In contrast, Marrache et al. [2] and Goh et al. [10] found that the frequency of coexistent IPMN/NET was higher than expected. According to the literature data, IPMN was seen in 2.9% (1/35) to 6.5% (3/46) of NET specimens [2, 7, 10], and NET was found in 1.1% (5/441) to 13.6% (3/22) of IPMN specimens [2, 3, 7, 8, 10, 12, 15]. In this study prevalence of NMA/NET among IPMN cases was higher that in previous reports (27%), and this number was related not only to the exact NMA/NET prevalence in the study population, but also to the preconceived diagnostic/screening approach.

Pathogenesis of NMA/NET in patients with IPMN

Little is known about pathogenesis of IPMN/NET coexistence. Some risk factors may be involved in development of both NET and IPMN. Diabetes, family history of cancer, and chronic pancreatitis increase the risk of both NET [21-23] and IPMN [24].

Molecular profiles of IPMN and NET are different [2], with exception of composite IPMN/NET [13, 14]. It was hypothesized that IPMN/NET forming a single lesion may develop from a common progenitor, or in transdifferentiation of a single cell type into another cell type [2, 7]. It was also speculated that NET may appear as a result of endocrine differentiation/hyperplasia within IPMN [10], but this hypothesis was not convincingly confirmed [2, 6]. Endocrine/paracrine stimulation of exocrine cells by NET-generated hormones may also play a role [11].

At the moment it is not possible to indicate exact reason(s) which lead to increased prevalence of NMA/NET in patients with IPMN. One may speculate that exocrine-endocrine cross-talk [25] is involved in pathogenesis of IPMN/NET coexistence. but this requires further study. Another hypothesis which could explain increased prevalence of NET/NMA in pancreata with IPMN is related to tissue remodeling, as seen in obstructive chronic pancreatitis/pancreatic atrophy. Histopathological features of obstructive pancreatitis are frequently seen in pancreata with IPMN (personal observation). Histopathological alterations of neuroendocrine cells have been recognized in pancreatic atrophy for decades [16, 17]. Chronic pancreatitis is considered a risk factor for NET development [22]. In the present study half of NMA in IPMN specimens was found within atrophic lobules. It is possible that diffuse obstructive atrophy in pancreata with IPMN could promote NET/NMA development (the issue under study).

In summary, IPMN and NET/NMA coexisting in the pancreas may be considered as:

- a single lesion with laboratory-confirmed common molecular alterations (composite tumor, common pathogenesis very likely),

- a single lesion in which laboratory tests excluded common molecular alterations (collision tumor, common pathogenesis unlikely),
- distinct lesions isolated by the uninvolved „normal" parenchyma (common pathogenesis highly unlikely),
- distinct lesions (sometimes diffuse and/or multiple) within severely altered pancreatic parenchyma, eg. in obstructive pancreatitis/atrophy (yet no data on common pathogenesis).

Study strength and limitations

The strength of the study was the design, based on prospective inclusion of totally embedded pancreatic specimens, which were examined histopathologically in an uniform fashion. To the best of our knowledge, this was the first report on IPMN/NET association based on prospectively examined, totally embedded pancreatic resection specimens.

Limitations of the study were the following:

- referral bias related to examination of surgical specimens (i.e. inclusion of relatively less advanced, potentially resectable PDAC cases as well as more advanced, suspected for cancer and/or symptomatic IPMN cases) [26],
- sampling bias related to anatomical distribution of IPMN/PDAC/AMPCA within pancreata,
- examination of only a portion of the pancreas in the majority of cases, as they were treated with partial pancreatecomy,
- setting-up of „control" groups using PDAC/AMPCA samples, rather than normal pancreata,
- diagnostic bias, as identification of one tumor (and subsequent pancreatic resection) resulted in extensive examination of the specimen towards identification of other lesions, and
- lack of clinical data on IPMN/NET risk factors in the study population.

Conclusions

The prevalence of NMA in pancreatic specimens with IPMN was 27% and it was significantly increased when compared to specimens with PDAC/AMPCA. Majority of NMA in IPMN specimens were solitary and localized within distal portion of the pancreas. Topographical association of IPMN and NMA was rare and no case in the present series showed features suggestive of composite (clonal) IPMN/NMA. IPMN/NMA association may serve as a model for investigation of exocrine-neuroendocrine interaction. Reasons for IPMN/NET coexistence are largely unknown and require further study.

Article information and declarations

Ethics statement

Institutional Review Board permitted to perform the present observational study without full review, which is necessary for interventional studies on humans, according to national regulations.

Author contributions

Manuscript prepared by a single author.

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Conflicts of Interest

None declared

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References

1. *WHO classification of tumors. Digestive system tumors.* Lyon; WHO, IARC; 2019.

2. Marrache F, Cazals-Hatem D, Kianmanesh R, et al. Endocrine tumor and intraductal papillary mucinous neoplasm of the pancreas: a fortuitous association? *Pancreas* 2005; 31: 79-83. doi: 10.1097/01.mpa.0000164453.46394.07

3. Partelli S, Giannone F, Schiavo Lena M, et al. Is the real prevalence of pancreatic neuroendocrine tumors underestimated? A retrospective study on a large series of pancreatic specimens. *Neuroendocrinology* 2019; 109: 165-170. doi: 10.1159/000499606

4. Manuel-Vazquez A, Ramia JM, Latorre-Fragua R, et al. Pancreatic neuroendocrine tumors and intraductal papillary mucinous neoplasm of the pancreas: a systematic review. *Pancreas* 2018; 47: 551-555. doi: 10.1097/MPA.0000000000001048

5. Moriyoshi K, Minamiguchi S, Miyagawa-Hayashino A, et al. Collision of extensive exocrine and neuroendocrine neoplasms in multiple endocrine neoplasia type 1 revealed by cytogenetic analysis of loss of heterozygosity: a case report. *Pathol Int* 2013; 63: 469-75. doi: 10.1111/pin.12088

6. Stukavec J, Jirasek T, Mandys V, et al. Poorly differentiated endocrine carcinoma and intraductal papillary-mucinous neoplasm of the pancreas: Description of an unusual case. *Pathol Res Pract* 2007; 203: 879-84. doi: 10.1016/j.prp.2007.08.012
7. Kadota Y, Shinoda M, Tanabe M, et al. Concomitant pancreatic endocrine neoplasm and intraductal papillary mucinous neoplasm: a case report and literature review. *World J Surg Oncol* 2013; 11: 75. doi: 10.1186/1477-7819-11-75
8. Sahora K, Crippa S, Zamboni G, et al. Intraductal papillary mucinous neoplasms of the pancreas with concurrent pancreatic and periampullary neoplasms. *Eur J Surg Oncol* 2016; 42: 197-204. doi: 10.1016/j.ejso.2015.10.014
9. Larghi A, Stobinski M, Galasso D, et al. Concomitant intraductal papillary mucinous neoplasm and pancreatic endocrine tumour: Report of two cases and review of the literature. *Dig Liver Dis* 2009; 41: 759-61. doi: 10.1016/j.dld.2009.01.005
10. Goh BK, Ooi LL, Kumarasinghe MP, et al. Clinicopathological features of patients with concomitant intraductal papillary mucinous neoplasm of the pancreas and pancreatic endocrine neoplasm. *Pancreatology* 2006; 6: 520-526. doi: 10.1159/000097361
11. Hashimoto Y, Murakami Y, Uemura K, et al. Mixed ductal-endocrine carcinoma derived from intraductal papillary mucinous neoplasm (IPMN) of the pancreas identified by human telomerase reverse transcriptase (hTERT) expression. *J Surg Oncol* 2008; 97: 469-75. doi: 10.1002/jso.20959
12. Gill KR, Scimeca D, Stauffer J, et al. Pancreatic neuroendocrine tumors among patients with intraductal papillary mucinous neoplasms: real association or just a coincidence? *JOP* 2009; 10: 515-7.
13. Schiavo Lena M, Cangi MG, et al. Evidence of a common cell origin in a case of pancreatic mixed intraductal papillary mucinous neoplasm-neuroendocrine tumor. *Virchows Arch* 2021; 478: 1215-1219. doi: 10.1007/s00428-020-02942-1
14. Chen J, Wang P, Lv K, et al. Case report: composite pancreatic intraductal papillary mucinous neoplasm and neuroendocrine tumor: a new mixed neuroendocrine-non-neuroendocrine neoplasm? *Diagn Pathol* 2021; 16: 108. doi: 10.1186/s13000-021-01165-5
15. Okawa Y, Tsuchikawa T, Hatanaka KC, et al. Clinical features of pancreatic neuroendocrine microadenoma: a single-center experience and literature review. *Pancreas* 2022; 51: 338-344. doi: 10.1097/MPA.0000000000002029
16. Kimura W, Kuroda A, Morioka Y. Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. *Dig Dis Sci* 1991; 36: 933-942. doi: 10.1007/BF01297144.
17. Bartow SA, Mukai K, Rosai J. Pseudoneoplastic proliferation of endocrine cells in pancreatic fibrosis. Cancer 1981; 47: 2627-2633. doi: 10.1002/1097-0142(19810601)47:11<2627::aid-cncr2820471118>3.0.co;2-c.
18. Lee MR, Harris C, Baeg KJ, et al. Incidence trends of gastroenteropancreatic neuroendocrine tumors in the United States. *Clin Gastroenterol Hepatol* 2019; 17: 2212-2217.e1. doi: 10.1016/j.cgh.2018.12.017

19. Grimelius L, Hultquist GT, Stenkvist B. Cytological differentiation of asymptomatic pancreatic islet cell tumours in autopsy material. *Virchows Arch* 1975; 365: 275-288. doi: 10.1007/BF00471177
20. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. *Endocr Pathol* 2022; 33: 115-154. doi: 10.1007/s12022-022-09708-
21. Leoncini E, Carioli G, La Vecchia C, et al. Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. *Ann Oncol* 2016; 27: 68-81. doi: 10.1093/annonc/mdv505
22. Capurso G, Falconi M, Panzuto F, et al. Risk factors for sporadic pancreatic endocrine tumors: a case-control study of prospectively evaluated patients. *Am J Gastroenterol* 2009; 104: 3034-3041. doi: 10.1038/ajg.2009.466
23. Feola T, Puliani G, Sesti F, et al. Risk factors for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs): a three-centric case-control study. *J Endocrinol Invest* 2022; 45: 849-857. doi: 10.1007/s40618-021-01715-0
24. Capurso G, Boccia S, Salvia R, et al. Risk factors for intraductal papillary mucinous neoplasm (IPMN) of the pancreas: a multicentre case-control study. *Am J Gastroenterol* 2013; 108: 1003-1009. doi: 10.1038/ajg.2013.42
25. Overton DL, Mastracci TL. Exocrine-Endocrine crosstalk: the influence of pancreatic cellular communications on organ growth, function and disease. *Front Endocrinol (Lausanne)* 2022; 13: 904004. doi: 10.3389/fendo.2022.904004
26. Kenig J, Richter P. Pancreatoduodenectomy due to cancer in the older population. *Nowotwory. Journal of Oncology* 2021; 71: 321-327. doi:10.5603/NJO.2021.0061

Figure 1. Neuroendocrine microadenoma (NMA) of the pancreas with partial intraductal spread but without direct contact with intraductal papillary mucinous neoplasm (IPMN) (sample no. 10).
NMA surrounding small duct (lower left of the image, lesion indicated by a rectangle) without direct relationship with IPMN (upper right of the image) (A). Partial intraductal spread of the NMA is seen at higher magnification (B). NMA showed chromogranin-A (not shown) and synaptophysin expression (C and D). Note synaptophysin-negative ductal cells above intraductal spread of neuroendocrine cells (D). Magnifications: fig. 1A (1.25x), 1B (5x), 1C (5x), 1D (30x)

Figure 2. Neuroendocrine microadenoma (NMA) in the atrophic pancreatic lobule surrounded by intraductal papillary mucinous neoplasm (IPMN) (sample no. 13). NMA was found in an atrophic lobule surrounded by gastric-type IPMN (A and B, lesion indicated b a rectangle) with partial intraductal tubular adenoma growth (not shown). NMA was glucagon-positive (C) and insulin-negative (D), and such hormone expression pattern excluded diagnosis of islet aggregation. Note insulin-positive cells in residual islets of the atrophic lobule (D). Magnifications: fig. 2A (3.5x), 2B (10x), 2C (10x), 2D (10x)

Figure 3. Neuroendocrine microadenomas (NMA) in other pancreatic specimens with intraductal papillary mucinous neoplasm (IPMN). Conventional NMA (indicated by a rectangle) in pancreatic parenchyma without relationship to IPMN (A and B). Another NMA (indicated by a rectangle) in pancreas with extensive atrophy. NMA was next to a duct with mucin leakage (C and D). NMA was chromogranin A-positive (not shown) and synaptophysin-positive (not shown). Magnifications: fig. 3A (3x), 3B (15x), 3C (2x), 3D (5x)

Table I. Clinico-pathological characteristics of the study cases

Characteristic	IPMN	Ductal carcinoma	Ampullary carcinoma	p value
no. of cases	51	114	67	NA
age (median; interquartile range)	66.5 (62–72)	66 (61–72)	67 (60–71)	0.756[1]
sex (male : female)	19 : 32	55 : 59	35 : 32	0.252[2]
surgery (PD : DP : TP : other)	14 : 16 : 19 : 2	83 : 30 : 1 : 0	65 : 0 : 2 : 0	<0.001[2]
tumor localization (head : distal pancreas : diffuse involvement)	22 : 17 : 12	84 : 30 : 0	67 : 0 : 0	<.001[2]
grade of dysplasia / presence of invasion: low-grade high-grade[3] Invasive carcinoma[4]	 8 17 26	only invasive tumors	only invasive tumors	NA
histological type of IPMN (based on predominant pattern): gastric intestinal pancreato-biliary oncocytic ITPN	 27 12 7 4 1	NA	NA	NA
diameter of invasive tumor (in mm; median; interquartile range)	17 (3–35)	31.5 (25–38)	15 (12–25)	<0.001[1]
Grade of invasive tumor: G1 G2 G3 G4	 17 5 4 0	 16 73 21 4	 11 37 19 0	<0.001[2]
histological type of invasive tumor: tubular colloid adenosquamous MINEN[5] mixed	 15 9 0 0 2[6]	 104 0 5 1 4[7]	 61 1 3 2 0	<0.001[2]
primary tumour stage:[8] pT1a pT1b pT1c	 9 1	 0 1	 4 13	<0.001[2, 9]

pT2 pT3 pT3a pT3b pT4	4 7 5 NA NA 0	9 76 23 NA NA 5	NA 9 NA 8 33 0	
regional nodal status:[8] pN0 pN1 pN2	 20 3 3	 14 28 72	 24 23 20	<0.001[2]
distant metastases:[8] cM0 cM1/pM1	 26 0	 105 9	 67 0	0.022[2]
number of tissue block (overall; median; interquartile range)	48 (34–69)	50 (43–61)	54 (47–61)	p = 0.199[1]
numer of tissue block containing pancreas (overall; median; interquartile range)	40 (30–61)	39 (33–45)	43 (37–50)	p = 0.072[1]

DP – distal pancreatectomy; IPMN – intraductal papillary mucinous neoplasm; ITPN – intraductal tubulopapillary neoplasm; NA – not applicable; PD – pancreatoduodenectomy; TP – total pancreatectomy; [1]Kruskal-Wallis ANOVA test; [2]chi2 test; [3]including cases of IPMN with concomitant high-grade pancreatic intraepithelial neoplasia (in the same specimen); [4]invasive carcinoma associated with IPMN or invasive carcinoma concomitant with IPMN (in the same specimen); [5]mixed neuroendocrine-nonneuroendocrine neoplasm; adenocarcinoma and large cell neuroendocrine carcinoma; [6]invasive carcinoma with both tubular and colloid differentiation; [7]adenocarcinoma/adenosquamous carcinoma with a component of undifferentiated carcinoma; [8]for invasive tumors only; according to American Joint Committee on Cancer 8th edition staging criteria (2017); [9]for statistical analysis, cases pT1a + pT1b + pT1c were grouped as pT1 category, and cases pT3a + pT3b were grouped as pT3 category

Table II. Neuroendocrine tumors / neuroendocrine microadenomas found in the study specimens

Number of cases	IPMN	Ductal carcinoma	Ampullary carcinoma	p value (chi2 tests)
with neuroendocrine tumors	1/51 (1.96%)	2/114 (1.75%)	1/67 (1.49%)	p = 0.981
with neuroendocrine microadenomas	14/51 (27.45%)	9/114 (7.89%)	5/67 (7.46%)	p < 0.001
overall number of cases with neuroendocrine tumors and/or neuroendocrine microadenomas	14/51 (27.45%)	10/114 (8.77%)	6/67 (8.96%)	p = 0.002

IPMN – intraductal papillary mucinous neoplasm

Table III. Comparison of IPMN with and without coexisting NMA/NET

Characteristic	IPMN with NET/NMA	IPMN without NET/NMA	p value
no. of cases	14	37	

age (median; interquartile range)	65.5 (62–70)	68 (62–72)	0.619[1]
sex (male : female)	4 : 10	15 : 22	p = 0.430[2]
surgery (PD : DP : TP : other)	1 : 5 : 8 : 0	13 : 11 : 11 : 2	p = 0.121[2]
localization of IPMN (head : distal pancreas : diffuse involvement)	1 : 5 : 8	21 : 12 : 4	p < 0.001[2]
grade of dysplasia / presence of invasion: low-grade high-grade[3] invasive carcinoma[4]	 3 5 6	 5 12 20	p = 0.709[2]
histological type of IPMN (based on predominant pattern): gastric intestinal pancreato-biliary oncocytic ITPN	 10 1 1 1 1	 17 11 6 3 0	p = 0.152[2]
diameter of invasive tumor (in mm; median; interquartile range)	3 (3–4)	25 (8.5–38.5)	0.007[1]
grade of invasive tumour: G1 G2 G3 G4	 5 1 0 0	 12 4 4 0	0.447[2]
histological type of invasive tumor: tubular colloid adenosquamous mixed	 5 1 0 0	 10 8 0 2[5]	0.330[2]
primary tumour stage:[6] pT1a pT1b pT1c pT2 pT3 pT4	 5 0 1 0 0 0	 4 1 3 7 5 0	0.055[2]
regional nodal status:[6] pN0 pN1 pN2	 6 0 0	 14 3 3	0.310[2]
distant metastases:[6] cM0 cM1	 6 0	 20 0	NA
number of tissue blocks (overall; median; interquartile range)	55.5 (34–71)	48 (34–66)	0.627[1]
numer of tissue blocks containing pancreas (overall; median; interquartile range)	46.5 (33–66)	40 (30–59)	0.527[1]

DP – distal pancreatectomy; IPMN – intraductal papiallary mucinous neoplasm; ITPN – intraductal tubulopapillary neoplasm; NA – not applicable; NET – neuroendocrine tumor; NMA – neuroendocrine micoradenoma; PD – pancreatoduodenectomy; TP – total pancreatectomy; [1] Mann-Whitney U test; [2] chi2 test; [3] including cases of IPMN with concomitant high-grade pancreatic intraepithelial neoplasia (in the same specimen); [4] invasive carcinoma associated with IPMN or invasive carcinoma concomitant with IPMN (in the same specimen); [5] invasive carcinoma with both tubular and colloid differentiation; [6] for invasive tumours only; according to American Joint Committee on Cancer 8th edition staging criteria (2017)

Table IV. Histopathological characteristics of IPMN coexisting with NMA/NET neoplasms

		IPMN									Neuroendocrine microadenoma					Neuroendocrine tumor					
no.	procedure	localization	diameter [mm]	histological type	dysplasia in IPMN	invasion	size of invasive carcinoma [mm]	type of invasive carcinoma	grade of invasive carcinoma	staging	number	localization	diameter [mm]	contact with duct or IPMN	localization in atrophic lobule	number	localization	diameter [mm]	grading	staging	connection with duct or IPMN
1.	TP	diffuse	diffuse	G	L	Y [1]	3	T	1	T1aN0M0	3	head	1 [2]	N	Y [3]	1	head	7	1	T1N0M0	N
2.	DP	distal	25	G	H	Y	3	T	1	T1aN0M0	1	distal	1.2	N	N	–	–	–	–	–	–
3.	DP	distal	10	G	L	N	–	–	–	–	1	distal	0.5	N	N	–	–	–	–	–	–
4.	DP	distal	20	G	L	N	–	–	–	–	1	distal	0.7	N	N	–	–	–	–	–	–
5.	TP	diffuse	diffuse	G	L	N	–	–	–	–	1	distal	0.5	N	N	–	–	–	–	–	–
6.	TP	diffuse	diffuse	O	H	N	–	–	–	TisN0M0	1	distal	0.6	N	Y	–	–	–	–	–	–
7.	PD	head	18	ITPN	H	Y	4	T	1	T1aN0M0	2	head	2 [2]	N	N	–	–	–	–	–	–
8.	TP	diffuse	diffuse	I	H	N	–	–	–	TisN0M0	6	head and distal	0.5-3	N	Y [3]	–	–	–	–	–	–

9.	TP	diffuse	diffuse	G	L	N	–	–	–	TisN0M0 [4]	5	distal	0.5-1	N	N	–	–	–	–	–	–
10.	TP	diffuse	diffuse	G	H	Y	3	T	2	T1aN0M0	1	head	3.8	Y[5]	Y	–	–	–	–	–	–
11.	TP	diffuse	diffuse	G	H	Y	1	C	1	T1aN0M0	1	head	0.6	N	N	–	–	–	–	–	–
12.	TP	diffuse	diffuse	G	H	N	–	–	–	TisN0M0	1	head	0.6	N	Y	–	–	–	–	–	–
13.	DP	distal	25	G	H	N	–	–	–	TisN0M0	1	distal	2.5	Y	Y	–	–	–	–	–	–
14.	DP	distal	80	PB	H	Y	12	T	1	T1cN0M0	1	distal	2	N	Y	–	–	–	–	–	–

C – colloid carcinoma; DP – distal pancreatectomy, distal – distal pancreas; G – gastric; H – high-grade IPMN; I – intestinal; IPMN – intraductal papillary mucinous neoplasm; ITPN – intraductal tubulopapillary neoplasm; L – low-grade IPMN; N – no; NET – neuroendocrine tumor; NMA – neuroendocrine microadenoma; O – oncocytic; PB – pancreatobiliary; PD – pancreatoduodenectomy; T – tubular adenocarcinoma; TP – total pancreatectomy; Y – yes; [1] invasive adenocarcinoma associated with non-dilated duct with high-grade pancreatic intraepithelial neoplasia; [2]each; [3]a single microadenoma in atrophic lobule; [4] concomitant high-grade pancreatic intraepithelial neoplasia; [5]partial intraductal spread - duct without IPMN; [6]NMA localized in atrophic lobule surrounded by IPMN lesion