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Management of small, asymptomatic, non-functioning pancreatic neuroendocrine tumours: follow-up, ablation, or surgery?

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Abstract

Non-functioning pancreatic neuroendocrine tumours (NF-pNETs) are potentially malignant neoplasms that are detected with increasing frequency. The management of small (≤ 2 cm) asymptomatic NF-pNETs remains an area of controversy and clinical dilemma. Follow-up seems to be a reasonable strategy because of the relatively limited metastatic potential of these tumours, the good clinical prognosis, and considering the high complication rate associated with surgery. However, some studies show metastatic potential of these tumours, fuelling an ongoing debate in the literature regarding their management. Making the decision to observe or perform surgery is thus not an easy task. New, promising therapeutic methods involving ablation under endoscopic ultrasound (EUS) guidance with ethanol or radiofrequency ablation have been applied for these lesions with good clinical outcomes but only with short-term follow-up data. In this review, we address the emerging question of when to follow-up and when to perform surgery for small asymptomatic pancreatic tumours, with consideration of the potential of ablative therapies. **(Endokrynol Pol 2023; 74 (1): 25–30)**

Key words: *pancreatic neuroendocrine tumour; ablation; EUS*

Pancreatic neuroendocrine tumours (pNETs) constitute up to 2% of pancreatic tumours and are detected with increasing frequency [1]. Most are sporadic, but they can develop as part of inherited syndromes, including multiple endocrine neoplasia 1 (MEN1), von Hippel-Lindau syndrome, and tuberous sclerosis [2–4]. These lesions are most commonly well-differentiated tumours with no hormonal activity, and their incidence increases with age [5]. The paucity of symptoms arising from their non-secreting nature is the primary reason they usually go undetected until they reach more advanced stages, compared with their functional counterparts. The overall 5-year survival in non-functional (NF)-pNETs is up to 43%, and median survival is 38 months. These survival metrics are much better than in pancreatic adenocarcinoma but still worse than in other gastrointestinal tumours such as colorectal cancer [6, 7].

Data indicate that the tumour size correlates with malignant potential, which in turn affects survival and mortality [8–10]. Bettini et al., using postoperative specimens, found that tumours measuring > 4 cm had significantly higher rates of microvascular invasion (26% *vs.* 13% for tumours < 2 cm) and of liver (4% *vs.* 0%) and nodal (20% *vs.* 13%) metastases [8]. The median antigen Ki-67 (Ki-67) value was 3% in tumours measuring > 4 cm compared with 2% for tumours of 2–3 cm and 1% for those < 2 cm [8]. The growth rate also depends on the size. An endoscopic ultrasound (EUS) study of 226 pNETs in patients with MEN1 syndrome showed an average growth rate of 0.1 mm per year, with no size progression in tumours measuring < 10 mm but progression of 0.44 mm/year in larger tumours [11].

Non-functioning sporadic tumours, which do not secrete hormones that cause clinical symptoms, are the most common type of pNETs and the focus of this review. The management of these tumours remains a clinical challenge and dilemma, largely because of uncertainty about their biology and factors related to malignant potential. Pancreatic surgery is complex and carries significant risk for complications including death, but taking a watch-and-wait approach risks development of metastases.

There is consensus among experts and guidelines that NF-pNETs < 1 cm can be safely followed up, taking into account their small metastatic potential reported in the literature [5, 12]. However, the European Neuroendocrine Tumour Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) guidelines are somewhat discrepant in their recommendation regarding when surgery should be performed for larger

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tumours. In their consensus guidelines, ENETS recommends surgery in G2, symptomatic pNETs, and tumours >2 cm [5]. This guidance is in line with Polish Network of Neuroendocrine Tumours recommendations [13]. Other researchers, considering the metastatic potential of NF-pNETs, have proposed 1.5 cm or 1.7 cm as a trigger for surgery [14, 15]. NANETS guidelines offer a much less conservative approach and recommend individualizing the decision for tumours measuring 1–2 cm, depending on patient age, comorbidities, tumour location, imaging features, change in size over time, access to follow-up, and the patient's wishes [12]. Table 1 presents the management recommendations for small NF-pNETs from the different societies.

Our knowledge of the metastatic potential of small pNETs is based either on pathological assessment of post-surgical material or on studies that have compared survival between patients treated surgically versus conservatively. Findings regarding small NF-pNETs have been mixed.

Some studies have shown indolent behaviour of small non-secreting pNETs, such as the findings of Gaujoux et al., who observed 46 patients with small NF-pNETs for a median of 34 months and found that none of the patients developed metastases [16]. Sadot et al. described a group of 104 patients with small asymptomatic neuroendocrine tumours and found no change in tumour size, no progression, and no mortality during a median 44 months of observation [17]. Lee et al. reported findings for 77 patients with small NF-pNETs who were treated conservatively compared with those for 56 patients who underwent surgery [18]. Neither group showed progression or disease-related mortality, but in the group treated with surgery, almost half of the patients had at least one post-operative complication (mainly pancreatic leak) [18].

REVIEW

Table 1. *Recommendations from different societies regarding the management of small (1–2 cm), asymptomatic, pancreatic, non-functioning, neuroendocrine tumours*

Guidelines		Follow-up
ENETS 2012, Update 2016 [5, 57]	In small, possibly benign tumours, the surgical risk benefit should be carefully weighed Update: tumor < 2 cm, option 1: surveillance (G1, low G2, asymptomatic, mainly in the head); option 2: surgery — G2, symptoms, patient wishes (5); a conservative approach seems to be safe because the majority of observed tumours did not show significant changes on follow-up (5)	Every 3 to 9 months
NANETS 2020 [58, 59]	Individualized decision: age comorbidities, tumour growth over time, estimated risk of symptom development, imaging features, grade, extent of surgical resection, patient wishes, access to follow-up	No consensus regarding follow-up for patients with resected pNETs < 2 cm; for larger tumours, 3 to 6 months after surgical resection
NCCN 2021 [60]	Observation (observation may be considered for low-grade, incidental, non-functioning tumours; decision based on surgical risk, tumour site, and patient comorbidities) *or* Enucleation ± lymphadenectomy *or* Resection ± lymphadenectomy	Provide post-resection recommendations: • 3–12 months in the first year • 1 year to 10 years after resection: 6–12 months • > 10 years: consider surveillance as clinically indicated
Polish Network of Neuroendocrine Tumours 2017 [13]	Accidentally detected, asymptomatic, non-functional neoplasms ≤ 2 cm in diameter, without evidence of histopathological and radiological malignancy may be observed, and the decision about the course of treatment should be taken by a multidisciplinary team of doctors experienced in the management of pNETs	3 months for NECs and 6–12 months for G1, G2, or G3 NETs, or more frequently if disease progression is suspected
Polish Network of Neuroendocrine Tumours (update) 2022 [61, 62]	Observation: G1 G2, with low Ki-67 (< 10%), ≤ 2 cm in size, with no radiographically identified malignancy can be observed: • optional surgery in NET of 1–2 cm tumours leaving the decisions to the therapeutic team and the patient • ablation performed under EUS control is an alternative treatment for NF-NETs G1/G2 with a diameter ≤ 2 cm, who are not candidates for surgery or refuse surgery	

ENETS — European Neuroendocrine Tumour Society; pNET — pancreatic neuroendocrine tumour; NANETS — North American Neuroendocrine Tumor Society; NCCN — National Comprehensive Cancer Network; NEC — neuroendocrine carcinoma; NET — neuroendocrine tumour; EUS — endosonography; NF-NET — non-functioning pancreatic neuroendocrine tumours; G — grading; Ki-67 — antigen Ki-67

In contrast to these findings that seem to favour conservative management, other groups have reported that the percentage of metastatic (mainly nodal) cases in patients who underwent surgery varies from 7% to 55% [19, 20]. Haynes et al. analysed the history of 39 patients after pancreatic surgery for NF-pNETs < 2 cm and found that 3 patients (7.7%) developed recurrence or late metastases [20]. In 158 patients with small asymptomatic pNETs and a follow-up of 45.6 months, Paik et al. found that 11 patients (7%) developed metastases or disease recurrence after surgery [21]. Jilesen et al. followed patients who had undergone pancreatoduodenectomy for neuroendocrine tumours < 2 cm and found on post-operative specimen analysis that 55% of the patients had lymph node metastases [19]. This result is in agreement with those of Finkelstein et al. and Sharpe et al., who reported better 5-year survival with surgery (82.2%) than with conservative management (34.3%) among patients with small pNETs [22, 23].

Taken together, the results overall indicate that small asymptomatic pNETs are a heterogenous group of tumours with uncertain biology, and that a cut-off of 2 cm for surgery may not be sufficient.

Researchers also are striving to identify both diagnostic and prognostic markers of pNETs. Apart from the obvious candidate factors such as number and extent of metastases in lymph node and liver and Ki-67 index, other prognostic markers have been proposed to indicate worse prognosis, including age, presence of symptoms, location in the pancreatic head or neck, presence of calcifications, and necrosis [13, 24]. It also has been suggested that the presence of cystic features on imaging is related to better prognosis and should be considered when making treatment decisions [4, 13, 24].

Contrast-enhanced EUS has gained attention as a potential tool for predicting the behaviour of NF-pNETs. Hyperenhancement is histopathologically related to fewer vessels and more fibrosis and was identified as a predictor of aggressive behaviour [25], and heterogeneous enhancement in the early arterial phase has been reported as a marker of G3 tumours and metastatic disease [26].

Recent studies of neuroendocrine tumours have identified some candidate molecular markers. Among those related to survival improvement are MEN1, mutations in the DAXX/ATRX protein [24, 27], and positive expression of somatostatin receptor (SSTR) type 2A (SSTR2A) and SSTR5. Telomere lengthening, in contrast, has been associated with worse survival and more aggressive tumour behaviour [24, 28–31].

The so-called liquid biopsy or NETest and its utility as a diagnostic marker of different types of neuroendocrine tumours, including pNETs, has been reported [32, 33]. The idea of liquid biopsy is to measure molecular markers of gene expression including messenger RNA (mRNA) in peripheral blood, which is said to be more accurate than the routinely used chromogranin A [34]. Another advantage of NETest is that it is not invasive and avoids the need for tissue biopsy. In studies, NETest values have been significantly more elevated in patients with disease progression, and the expression of some microRNAs has been reported as a marker of tumour aggressiveness and patient survival [24, 33]. These markers have yet to become a routine part of clinical practice.

A factor that cannot be underestimated in decision-making about pNET management is the risk of adverse events related to pancreatic surgery. Pancreatic head surgery (pancreaticoduodenectomy, or Whipple's procedure) remains one of the most complex abdominal surgeries, sometimes described as the "Cadillac of abdominal surgery". It carries a mortality of 3% and overall complication rate of 52% [35, 36]. For these reasons, the qualifying criteria for surgery should go beyond infiltration of vessels and the presence of metastases, and include the patient's general health condition, age, and comorbidities.

Enucleation is less invasive than pancreaticoduodenectomy and recommended by the ENETS guidelines. Jilesen et al. compared surgical complication rates and outcomes among enucleation, pancreaticoduodenectomy, and distal pancreatic resection in pNETs [19]. The overall complication, readmission, and intervention rates were comparable for both methods of pancreatic head tumour treatment, but pancreatic exocrine and endocrine insufficiency were more common after pancreatoduodenectomy [19].

The same authors conducted a systematic review of 62 studies of surgically treated patients with pNETs (37) and found that, depending on the type of surgery, pancreatic surgery was related to a 3–6% overall mortality, 1–7% risk of bleeding, 5–18% risk of delayed gastric emptying, and 14%–58% risk of fistula. Fistula was the most common complication and was more common in patients after enucleation (45%) than after distal pancreatic resection or pancreaticoduodenectomy [37].

Apart from surgery, endoscopic ablative methods of treatment, including ethanol and radiofrequency ablation, seem to be promising alternatives for the management of small pNETs. The history of using ablation for pNETs can be traced back to a first report by Jurgensen et al. in 2006, who described the successful ethanol ablation of a pancreatic insulinoma. Since that time, this method of treatment has gained considerable attention, with many cases described [38–40]. Our review of 27 cases of insulinoma treated with ethanol ablation showed high effectiveness (reaching 100%) and safety. We identified only one major complication

[41], probably due to use of a low ethanol concentration, and highlighted some technical issues that need to be addressed, including choosing the best needle gauge and the volume and concentration of ethanol [39].

El Sayed et al. reviewed outcomes for 75 patients with insulinoma, 47 of whom were treated with ethanol ablation, 27 with radiofrequency ablation, and one with both methods. The authors found that both methods were safe and effective, with an overall success rate of 98.5% [42]. Complications of concern, apart from mild self-limiting pancreatitis, were delayed ulceration of the duodenal wall with hematoma and stricture of the pancreatic duct, both of which were resolved endoscopically [43].

Limitations of alcohol ablation include less effectiveness in the treatment of NF-pNETs and safety concerns. Apart from the risk of mainly self-limiting pancreatitis, which develops in 6% to 12% of cases, ethanol ablation may result in other complications such as bleeding, strictures of the pancreatic or bile ducts, or secondary biliary sclerosing cholangitis [44]. Experience with ethanol ablation of NF-pNETs and its effectiveness in this patient population is limited compared with studies involving functional pNETs. Park et al. reported on the response to ablation among 10 patients with small NF-pNETs. They defined success as the radiologic disappearance of enhancing elements at the 3-month follow-up, which occurred in 60% of cases [40]. Armellini [45] suggested possible reasons for this lower effectiveness, including more advanced grading of NF-pNETs at detection or a debulking effect resulting from secretion in functioning pNETs. Figure 1 shows the typical endosonographic image of a pancreatic neuroendocrine tumour.

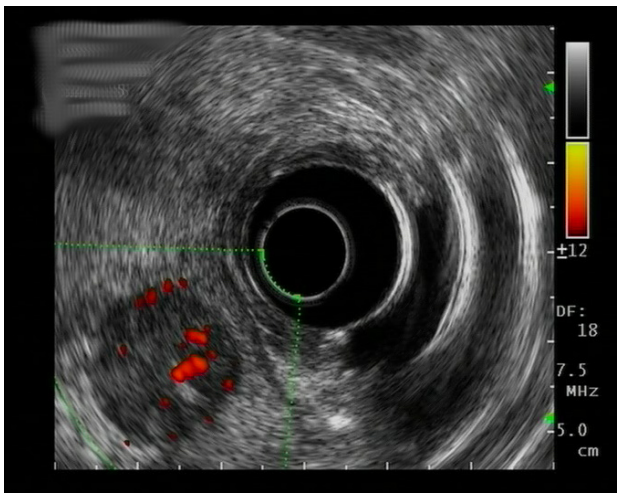

Figure 1. *Typical image of pancreatic neuroendocrine tumour seen in radial endosonography (EUS). Small, 17 mm, hypoechoic, well-defined, and vascularized lesion*

Radiofrequency ablation relies on delivery of a high-frequency alternating current through a needle or needle-like device, which heats the tissue and triggers tumour necrosis [46, 47]. The reports describe the effectiveness of radiofrequency ablation in different types of tumours including hepatocellular carcinoma, well-differentiated thyroid, and medullary cancer [48], and different types of pancreatic tumours, including cystic neoplasms and cancer [49, 50]. Current experience with EUS-guided radiofrequency ablation of NF-pNETs is limited mainly to case reports and series [51–53]. Barthet et al. presented the long-term outcomes of radiofrequency ablation of small NF-pNETs with promising results. They found that 12 of 14 lesions completely disappeared, although 2 failures were noted. One was a recurrence after the initial disappearance of the lesion after one year, and the second involved no initial response to the treatment and development of metastases [49]. The overall complication rate was 13.79%, and complications were pancreatitis, perforation in a patient with a cystic lesion, one biliary leakage, and pancreatic duct stenosis. This rate fell to 7.3% when nonsteroidal anti-inflammatory drugs and antibiotic prophylaxis were used before the procedure [49].

The largest data source on ablation of NF-pNETs is a meta-analysis by Zhang [54]. This analysis of 14 studies with 158 patients (78 with NF-pNETs, 26 insulinomas) compared the effectiveness and safety of both ablative approaches. The clinical success rate was higher for ethanol ablation (87.9% *vs*. 83.5% for radiofrequency ablation), and the overall complication rate was lower for ethanol ablation (21.2% *vs*. 32.2% for radiofrequency ablation). Most complications were early and self-limiting and included abdominal pain, pancreatitis, peripancreatic fluid collections, and hyperamylasaemia. Among the few (n = 6) late complications were jaundice, pancreatic duct stenosis, duodenal stricture, and cystic fluid collection [54]. The advantages of ethanol ablation are also its accessibility, low cost, and lack of need for special equipment in comparison with radiofrequency ablation.

Ethanol and radiofrequency ablation are gaining increasing attention for the management of small pNETs. The feasibility, accessibility, and safety of these methods allows anticipation of their application more broadly in the treatment of these lesions. The differential malignancy potential identified in studies suggests heterogeneity of pNETs and emphasizes the currently limited understanding of their molecular biology. Some ongoing multicentre, large, prospective, observational studies may shed some light on the biology of small pNETs (ASPEN, PANDORA) [55, 56]. It should be underlined that the recently published update of the Polish Network of Neuroendocrine Tumours guidelines

sets the place for ablative therapies as an alternative treatment for patients with NF-NETs G1/G2 with a diameter ≤ 2 cm, who are not candidates for or refuse surgery [61, 62].

The limited number of available studies indicates that small asymptomatic NF-pNETs may show aggressive behaviour and that size is not a sufficient criterion for decision-making about management. Further research should aim at improved molecular characterization of pNETs measuring 1–2 cm to allow for better prediction of which tumours have metastatic potential. While we cannot predict the biology of the tumour, we should adhere to current rules calling for imaging follow-up for neoplasms < 1 cm and surgery for tumours > 2 cm, leaving a grey area for tumours that are 1–2 cm but for which ablative therapies may be offered. Ablative therapies are also a good option for patients who do not qualify for or who refuse surgery. Factors to consider regarding surgery include the patient's wishes, age, comorbidities, and tumour location. No clear recommendations cover which method of ablation should be applied, and multicentre and prospective studies with long-term follow-up are needed to confirm the long-term efficacy of ablative therapies.

Conflict of interest

None declared.

References

1. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017; 3(10): 1335–1342, doi: 10.1001/jamaoncol.2017.0589, indexed in Pubmed: 28448665.
2. Koniusz J, Dąbkowski K, Buczek K, et al. [Gastroenterological manifestations of von Hippel-Lindau disease]. Pol Merkur Lekarski. 2017; 43(254): 53–55, indexed in Pubmed: 28875969.
3. Koniusz J, Dąbkowski K, Buczek K, et al. [Gastroenterological manifestations of von Hippel-Lindau disease - a case report]. Pol Merkur Lekarski. 2017; 43(254): 66–68, indexed in Pubmed: 28875972.
4. Dąbkowski K, Kos-Kudła B, Andrysiak-Mamos E, et al. Cystic pancreatic neuroendocrine tumours - a gastroenterologist's point of view. Endokrynol Pol. 2018; 69(3): 320–325, doi: 10.5603/EP.2018.0034, indexed in Pubmed: 29952422.
5. Falconi M, Eriksson B, Kaltsas G, et al. Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016; 103(2): 153–171, doi: 10.1159/000443171, indexed in Pubmed: 26742109.
6. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008; 26(18): 3063–3072, doi: 10.1200/JCO.2007.15.4377, indexed in Pubmed: 18565894.
7. Săftoiu A, Hassan C, Areia M, et al. Role of gastrointestinal endoscopy in the screening of digestive tract cancers in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2020; 52(4): 293–304, doi: 10.1055/a-1104-5245, indexed in Pubmed: 32052404.
8. Bettini R, Partelli S, Boninsegna L, et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. Surgery. 2011; 150(1): 75–82, doi: 10.1016/j.surg.2011.02.022, indexed in Pubmed: 21683859.
9. Scarpa A, Mantovani W, Capelli P, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. Mod Pathol. 2010; 23(6): 824–833, doi: 10.1038/modpathol.2010.58, indexed in Pubmed: 20305616.
10. Gullo L, Migliori M, Falconi M, et al. Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. Am J Gastroenterol. 2003; 98(11): 2435–2439, doi: 10.1111/j.1572-0241.2003.07704.x, indexed in Pubmed: 14638345.
11. Kappelle WFW, Valk GD, Leenders M, et al. Growth rate of small pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1: results from an endoscopic ultrasound based cohort study. Endoscopy. 2017; 49(1): 27–34, doi: 10.1055/s-0042-119402, indexed in Pubmed: 27975336.
12. Howe JR, Merchant NB, Conrad C, et al. The North American Neuroendocrine Tumor Society Consensus Paper on the Surgical Management of Pancreatic Neuroendocrine Tumors. Pancreas. 2020; 49(1): 1–33, doi: 10.1097/MPA.0000000000001454, indexed in Pubmed: 31856076.
13. Kos-Kudła B, Rosiek V, Borowska M, et al. Pancreatic neuroendocrine neoplasms - management guidelines (recommended by the Polish Network of Neuroendocrine Tumours). Endokrynol Pol. 2017; 68: 169–97, doi: 10.5603/EP.2017.2016, indexed in Pubmed: 24431118.
14. Regenet N, Carrere N, Boulanger G, et al. Is the 2-cm size cutoff relevant for small nonfunctioning pancreatic neuroendocrine tumors: A French multicenter study. Surgery. 2016; 159(3): 901–907, doi: 10.1016/j.surg.2015.10.003, indexed in Pubmed: 26590096.
15. Kishi Y, Shimada K, Nara S, et al. Basing treatment strategy for non-functional pancreatic neuroendocrine tumors on tumor size. Ann Surg Oncol. 2014; 21(9): 2882–2888, doi: 10.1245/s10434-014-3701-y, indexed in Pubmed: 24740828.
16. Gaujoux S, Partelli S, Maire F, et al. Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. J Clin Endocrinol Metab. 2013; 98(12): 4784–4789, doi: 10.1210/jc.2013-2604, indexed in Pubmed: 24057286.
17. Sadot E, Reidy-Lagunes DL, Tang LH, et al. Observation versus Resection for Small Asymptomatic Pancreatic Neuroendocrine Tumors: A Matched Case-Control Study. Ann Surg Oncol. 2016; 23(4): 1361–1370, doi: 10.1245/s10434-015-4986-1, indexed in Pubmed: 26597365.
18. Lee LC, Grant CS, Salomao DR, et al. Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): role for nonoperative management. Surgery. 2012; 152(6): 965–974, doi: 10.1016/j.surg.2012.08.038, indexed in Pubmed: 23102679.
19. Jilesen APJ, van Eijck CHJ, Busch ORC, et al. Postoperative Outcomes of Enucleation and Standard Resections in Patients with a Pancreatic Neuroendocrine Tumor. World J Surg. 2016; 40(3): 715–728, doi: 10.1007/s00268-015-3341-9, indexed in Pubmed: 26608956.
20. Haynes AB, Deshpande V, Ingkakul T, et al. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. Arch Surg. 2011; 146(5): 534–538, doi: 10.1001/archsurg.2011.102, indexed in Pubmed: 21576607.
21. Paik WH, Lee HS, Lee KJ, et al. Malignant potential of small pancreatic neuroendocrine neoplasm and its risk factors: A multicenter nationwide study. Pancreatology. 2021; 21(1): 208–214, doi: 10.1016/j.pan.2020.11.016, indexed in Pubmed: 33281058.
22. Finkelstein P, Sharma R, Picado O, et al. Pancreatic Neuroendocrine Tumors (panNETs): Analysis of Overall Survival of Nonsurgical Management Versus Surgical Resection. J Gastrointest Surg. 2017; 21(5): 855–866, doi: 10.1007/s11605-017-3365-6, indexed in Pubmed: 28255853.
23. Sharpe SM, In H, Winchester DJ, et al. Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. J Gastrointest Surg. 2015; 19(1): 117–23; discussion 123, doi: 10.1007/s11605-014-2615-0, indexed in Pubmed: 25155459.
24. Gao Y, Gao H, Wang G, et al. A meta-analysis of Prognostic factor of Pancreatic neuroendocrine neoplasms. Sci Rep. 2018; 8(1): 7271, doi: 10.1038/s41598-018-24072-0, indexed in Pubmed: 29739948.
25. Ishikawa R, Kamata K, Hara A, et al. Utility of contrast-enhanced harmonic endoscopic ultrasonography for predicting the prognosis of pancreatic neuroendocrine neoplasms. Dig Endosc. 2021; 33(5): 829–839, doi: 10.1111/den.13862, indexed in Pubmed: 33020955.
26. Palazzo M, Napoléon B, Gincul R, et al. Contrast harmonic EUS for the prediction of pancreatic neuroendocrine tumor aggressiveness (with videos). Gastrointest Endosc. 2018; 87(6): 1481–1488, doi: 10.1016/j.gie.2017.12.033, indexed in Pubmed: 29325706.
27. Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science. 2011; 331(6021): 1199–1203, doi: 10.1126/science.1200609, indexed in Pubmed: 21252315.
28. Brunner P, Jörg AC, Glatz K, et al. The prognostic and predictive value of sstr-immunohistochemistry and sstr-targeted imaging in neuroendocrine tumors. Eur J Nucl Med Mol Imaging. 2017; 44(3): 468–475, doi: 10.1007/s00259-016-3486-2, indexed in Pubmed: 27539020.
29. Okuwaki K, Kida M, Mikami T, et al. Clinicopathologic characteristics of pancreatic neuroendocrine tumors and relation of somatostatin receptor type 2A to outcomes. Cancer. 2013; 119(23): 4094–4102, doi: 10.1002/cncr.28341, indexed in Pubmed: 24022344.
30. Wang Y, Wang W, Jin K, et al. Somatostatin receptor expression indicates improved prognosis in gastroenteropancreatic neuroendocrine neoplasm, and octreotide long-acting release is effective and safe in Chinese patients with advanced gastroenteropancreatic neuroendocrine

tumors. Oncol Lett. 2017; 13(3): 1165–1174, doi: 10.3892/ol.2017.5591, indexed in Pubmed: 28454229.
31. Kim JY, Brosnan-Cashman JA, An S, et al. Alternative Lengthening of Telomeres in Primary Pancreatic Neuroendocrine Tumors Is Associated with Aggressive Clinical Behavior and Poor Survival. Clin Cancer Res. 2017; 23(6): 1598–1606, doi: 10.1158/1078-0432.CCR-16-1147, indexed in Pubmed: 27663587.
32. Modlin IM, Kidd M, Falconi M, et al. A multigenomic liquid biopsy biomarker for neuroendocrine tumor disease outperforms CgA and has surgical and clinical utility. Ann Oncol. 2021; 32(11): 1425–1433, doi: 10.1016/j.annonc.2021.08.1746, indexed in Pubmed: 34390828.
33. Malczewska A, Witkowska M, Makulik K, et al. NETest liquid biopsy is diagnostic of small intestine and pancreatic neuroendocrine tumors and correlates with imaging. Endocr Connect. 2019 [Epub ahead of print], doi: 10.1530/EC-19-0030, indexed in Pubmed: 30865931.
34. Modlin IM, Kidd M, Malczewska A, et al. The NETest: The Clinical Utility of Multigene Blood Analysis in the Diagnosis and Management of Neuroendocrine Tumors. Endocrinol Metab Clin North Am. 2018; 47(3): 485–504, doi: 10.1016/j.ecl.2018.05.002, indexed in Pubmed: 30098712.
35. Moossa AR. Reoperation for pancreatic cancer. Arch Surg. 1979; 114(4): 502–504, doi: 10.1001/archsurg.1979.01370280156025, indexed in Pubmed: 435064.
36. Ricci C, Taffurelli G, Campana D, et al. Is surgery the best treatment for sporadic small (≤2 cm) non-functioning pancreatic neuroendocrine tumours? A single centre experience. Pancreatology. 2017; 17(3): 471–477, doi: 10.1016/j.pan.2017.03.004.
37. Jilesen APJ, van Eijck CHJ, in't Hof KH, et al. Postoperative Complications, In-Hospital Mortality and 5-Year Survival After Surgical Resection for Patients with a Pancreatic Neuroendocrine Tumor: A Systematic Review. World J Surg. 2016; 40(3): 729–748, doi: 10.1007/s00268-015-3328-6, indexed in Pubmed: 26661846.
38. Jürgensen C, Schuppan D, Neser F, et al. EUS-guided alcohol ablation of an insulinoma. Gastrointest Endosc. 2006; 63(7): 1059–1062, doi: 10.1016/j.gie.2005.10.034, indexed in Pubmed: 16733126.
39. Dąbkowski K, Gajewska P, Walter K, et al. Successful EUS-guided ethanol ablation of insulinoma, four-year follow-up. Case report and literature review. Endokrynol Pol. 2017; 68(4): 472–479, doi: 10.5603/EP.2017.0053, indexed in Pubmed: 28819950.
40. Park DoH, Choi JH, Oh D, et al. Endoscopic ultrasonography-guided ethanol ablation for small pancreatic neuroendocrine tumors: results of a pilot study. Clin Endosc. 2015; 48(2): 158–164, doi: 10.5946/ce.2015.48.2.158, indexed in Pubmed: 25844345.
41. Muscatiello N, Salcuni A, Macarini L, et al. Treatment of a pancreatic endocrine tumor by ethanol injection (PEI) guided by endoscopic ultrasound. Endoscopy. 2008; 40 Suppl 2: E83–E259, doi: 10.1055/s-2007-995540, indexed in Pubmed: 18633893.
42. El Sayed G, Frim L, Franklin J, et al. Endoscopic ultrasound-guided ethanol and radiofrequency ablation of pancreatic insulinomas: a systematic literature review. Therap Adv Gastroenterol. 2021; 14: 17562848211042171, doi: 10.1177/17562848211042171, indexed in Pubmed: 34819995.
43. Deprez PH, Claessens A, Borbath I, et al. Successful endoscopic ultrasound-guided ethanol ablation of a sporadic insulinoma. Acta Gastroenterol Belg. 2008; 71(3): 333–337, indexed in Pubmed: 19198582.
44. Bronswijk M. Endoscopic ultrasound-guided ablation of pancreatic neuroendocrine tumors: with or without alcohol? Endoscopy. 2019; 51(8): 798, doi: 10.1055/a-0889-8106, indexed in Pubmed: 31344735.
45. Armellini E, Crinò SF, Ballarè M, et al. Endoscopic ultrasound-guided ethanol ablation of pancreatic neuroendocrine tumours: A case study and literature review. World J Gastrointest Endosc. 2016; 8(3): 192–197, doi: 10.4253/wjge.v8.i3.192, indexed in Pubmed: 26862370.
46. Afzal MR, Samanta A, Shah ZI, et al. Adult Bone Marrow Cell Therapy for Ischemic Heart Disease: Evidence and Insights From Randomized Controlled Trials. Circ Res. 2015; 117(6): 558–575, doi: 10.1161/CIRCRESAHA.114.304792, indexed in Pubmed: 26160853.
47. Lakhtakia S. Therapy of Pancreatic Neuroendocrine Tumors: Fine Needle Intervention including Ethanol and Radiofrequency Ablation. Clin Endosc. 2017; 50(6): 546–551, doi: 10.5946/ce.2017.167, indexed in Pubmed: 29207860.
48. Chegeni H, Ebrahiminik H, Mosadegh Khah A, et al. Ultrasound-Guided Radiofrequency Ablation of Locally Recurrent Thyroid Carcinoma. Cardiovasc Intervent Radiol. 2022; 45(5): 677–684, doi: 10.1007/s00270-021-03042-6, indexed in Pubmed: 35066613.
49. Barthet M, Giovannini M, Gasmi M, et al. Long-term outcome after EUS-guided radiofrequency ablation: Prospective results in pancreatic neuroendocrine tumors and pancreatic cystic neoplasms. Endosc Int Open. 2021; 9(8): E1178–E1185, doi: 10.1055/a-1479-2199, indexed in Pubmed: 34447860.
50. Song TJ, Seo DW, Lakhtakia S, et al. Initial experience of EUS-guided radiofrequency ablation of unresectable pancreatic cancer. Gastrointest Endosc. 2016; 83(2): 440–443, doi: 10.1016/j.gie.2015.08.048, indexed in Pubmed: 26344883.
51. Armellini E, Crinò SF, Ballarè M, et al. Endoscopic ultrasound-guided radiofrequency ablation of a pancreatic neuroendocrine tumor. Endoscopy. 2015; 47 Suppl 1 UCTN: E600–E601, doi: 10.1055/s-0034-1393677, indexed in Pubmed: 26671543.
52. Pai M, Habib N, Senturk H, et al. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J Gastrointest Surg. 2015; 7(4): 52–59, doi: 10.4240/wjgs.v7.i4.52, indexed in Pubmed: 25914783.
53. Ligresti D, Amata M, Barresi L, et al. EUS-guided radiofrequency ablation of small pancreatic adenocarcinoma: a new therapeutic option for patients unfit for surgery. VideoGIE. 2019; 4(1): 29–31, doi: 10.1016/j.vgie.2018.09.008, indexed in Pubmed: 30623157.
54. Zhang Lu, Tan S, Huang S, et al. The safety and efficacy of endoscopic ultrasound-guided ablation therapy for solid pancreatic tumors: a systematic review. Scand J Gastroenterol. 2020; 55(9): 1121–1131, doi: 10.1080/00365521.2020.1797870, indexed in Pubmed: 32730715.
55. Heidsma CM, Engelsman AF, van Dieren S, et al. Watchful waiting for small non-functional pancreatic neuroendocrine tumours: nationwide prospective cohort study (PANDORA). Br J Surg. 2021; 108(8): 888–891, doi: 10.1093/bjs/znab088, indexed in Pubmed: 33783475.
56. Partelli S, Ramage JK, Massironi S, et al. Management of Asymptomatic Sporadic Nonfunctioning Pancreatic Neuroendocrine Neoplasms (ASPEN) ≤2 cm: Study Protocol for a Prospective Observational Study. Front Med (Lausanne). 2020; 7: 598438, doi: 10.3389/fmed.2020.598438, indexed in Pubmed: 33425946.
57. Falconi M, Bartsch DK, Eriksson B, et al. Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. Neuroendocrinology. 2012; 95(2): 120–134, doi: 10.1159/000335587, indexed in Pubmed: 22261872.
58. Howe JR, Merchant NB, Conrad C, et al. The North American Neuroendocrine Tumor Society Consensus Paper on the Surgical Management of Pancreatic Neuroendocrine Tumors. Pancreas. 2020; 49(1): 1–33, doi: 10.1097/MPA.0000000000001454, indexed in Pubmed: 31856076.
59. Halfdanarson TR, Strosberg JR, Tang L, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors. Pancreas. 2020; 49(7): 863–881, doi: 10.1097/MPA.0000000000001597, indexed in Pubmed: 32675783.
60. Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw. 2018; 16(6): 693–702, doi: 10.6004/jnccn.2018.0056, indexed in Pubmed: 29891520.
61. Kos-Kudła B, Foltyn W, Malczewska A, et al. Update of the diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours. Endokrynol Pol. 2022; 73(3): 387–454, doi: 10.5603/EP.a2022.0049, indexed in Pubmed: 36059171.
62. Kos-Kudła B, Rosiek V, Borowska M, et al. Pancreatic neuroendocrine neoplasms — update of the diagnostic and therapeutic guidelines (recommended by the Polish Network of Neuroendocrine Tumours). Endokrynol Pol. 2022; 73(3): 491–548, doi: 10.5603/EP.a2022.0050, indexed in Pubmed: 36059173.