Research Square

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Surgery does not have a role in all pancreatic neuroendocrine tumors

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Abstract

Background

The diagnosis of small, non-functioning pancreatic neuroendocrine tumors (pNETs) has increased due to the widespread use of abdominal imaging. However, pancreatic surgery carries significant risks of morbidity and mortality, prompting interest in non-operative management for biologically favorable, small pNETs.

Aim

To evaluate the long-term outcomes of patients with small, non-functioning pNETs (< 2 cm, Ki67 < 5%, no lymph node involvement or metastasis) managed non-operatively and compare them to outcomes of similar patients who underwent surgical resection.

Methods

This retrospective cohort study at a tertiary referral center compared surgery and surveillance in small non-functioning pNETs (≤ 2 cm, asymptomatic, well-differentiated, grade 1–2, Ki-67 < 5%, no nodal/distant disease). Patients diagnosed 2007–2023 with ≥ 24 months follow-up were analyzed. Groups were compared for diagnostics, metastasis, survival, and recurrence using descriptive statistics. The study followed STROBE guidelines and was approved by the xxx University, xxx Faculty of Medicine Ethics Committee Date: 28.11.2025, Decision No: 24, Protocol No: 2025/2002).

Results

Patients with < 2 cm, non-functioning, Ki67 < 5% pNETs and ≥ 24 months follow-up were included. Ten patients (median age: 50 years) underwent curative resection, with no recurrences during a mean follow-up of 107 months (range: 24–223 months). Nine patients (median age: 59 years) were managed non-operatively, with no tumor progression, NSE elevation, lymph node involvement, or distant metastasis during a mean follow-up of 47 months (range: 24–87 months).

Conclusion

Non-operative management of biologically favorable pNETs is a safe and effective alternative to surgery, sparing patients from the morbidity and mortality associated with pancreatic surgery.

MAIN POINTS

· Active surveillance of biologically favorable (Ki-67 <5%) small NF-pNETs (<2 cm) is a safe alternative to surgical resection.

· No progression, nodal disease, or metastasis occurred during follow-up.

· Surgery provides excellent long-term results but with higher morbidity.

· Active surveillance offers oncologic safety comparable to surgery.

INTRODUCTION

Pancreatic neuroendocrine neoplasms (p-NETs), arise from the islet cells, account for 1–2% of all pancreatic tumors, with 80% non-functioning [1]. The incidence of pancreatic NETs has significantly increased recently due to the incidental detection of small, asymptomatic lesions with widely used imaging tools [2, 3]. The biological behavior of p-NETs is highly heterogeneous and depends on factors such as tumor size, grade, stage, and overall tumor burden [4, 5, 6]. In small, well-differentiated, and biologically indolent tumors, the risk of lymph node involvement or distant metastasis is considered to be very low [7, 8]. Neverthless, recommended treatment is pancreatic resection which is associated with high morbidity and mortality [9, 10].

The growing incidence of incidentally detected, small, asymptomatic p-NETs on abdominal imaging performed for unrelated reasons has necessitated individualized, risk-adapted strategies. Given the risks of surgery, "watch-and-wait" strategy is increasingly considered for asymptomatic, non-functional p-NETs measuring ≤ 2 cm with favorable biological features. In this context, it is important to adopt conservative management protocols to minimize the risk of overtreatment and prevent complications [7, 11, 12]. Notably, in a contemporary nationwide NCDB analysis of 4,023 patients with 1–2 cm well-differentiated NF-PNETs, 25.6% were managed with observation; overall survival with observation was comparable to surgery except when a true R0 resection was achieved (and, among resections, the signal was largely confined to distal pancreatectomy), supporting surveillance as a reasonable strategy in carefully selected patients [13]. Accordingly, a non-operative management protocol was developed in our clinic in select patients.

This study aims to compare the outcomes of patients with small non-functioning tumors managed according to the conservative follow-up protocol against surgical treatment.

MATERIALS AND METHODS

The study protocol was approved by the xxx University, xxx Faculty of Medicine Ethics Committee (Date: 28.11.2025, Decision No: 24, Protocol No: 2025/2002). The study was

conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study Design and Population

This was a retrospective cohort study conducted at a tertiary referral center, comparing conservative treatment against surgical resection in patients diagnosed with small non-functioning pancreatic neuroendocrine tumors. Patients diagnosed and treated between January 2007 and May 2023 and completed 24-month follow-up was included. The non-operative management protocol, implemented in 2018, consists of the following criteria;

- Tumor diameter ≤ 2 cm,
- Asymptomatic,
- Non-functioning,
- Absence of lymph node involvement and distant metastasis,
- Well-differentiated histological subtype,
- Grade 1 or 2 tumors,
- Ki-67 proliferation index $< 5\%$

Surgical cohort was selected from patients with similar characteristics who were subjected to surgery prior to the implementation of the non-operative management protocol, as well as those who refused conservative follow-up. Patient demographics and diagnostic methods were assessed. Baseline characteristics of both groups are summarized in Table 1. Groups were compared in terms of development of lymph node or distant metastases and overall survival. Disease progression was evaluated in the non-operative treatment group, as well as postoperative complications, hospital stay and recurrence after surgery.

Table 1
Baseline characteristics of the patients.

Variable	Non-operative (n = 9)	Surgical Resection (n = 10)
Median age, years (range)	59 (34–75)	50 (29–68)
Sex, female:male	5:4	4:6
Median tumor size, mm (range)	13 (8–19)	14 (8–20)
Tumor grade (G1/G2)	8/1	2/8
Median Ki-67 index, % (range)	2 (1–8)	3 (1–5)

Statistical Analysis

Data were analyzed using descriptive statistical methods. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), and categorical variables were presented as frequencies and percentages (%). Due to the descriptive nature of the study and the specific cohort size, comparative statistical tests were not performed. All analyses were conducted using Microsoft Excel 2021 (Microsoft Corp., Redmond, WA, USA).

FINDINGS

Non-operative management group:

The non-operative management cohort consisted of nine patients (six females, three males) with a median age of 59 years (range: 34–75) (Table 1). Eight lesions were incidentally diagnosed, while one patient was identified during follow-up for Von Hippel-Lindau syndrome. Imaging modalities included computed tomography (CT) in six patients and magnetic resonance imaging (MRI) in seven patients. Ga-68 PET scans revealed somatostatin receptor expression in every lesion (Fig. 1). Tumors were evenly distributed between the pancreatic head (n = 5) and body (n = 4). No lymph node involvement, distant metastases or pancreatic duct dilatation were detected in the imagings.

At diagnosis, the mean NSE level was 15 ng/mL (range: 9–23 ng/mL; reference range: 0–16.3 ng/mL). Chromogranin A (CgA) levels were available in five patients, with a mean value of 102.2 ng/mL (range: 21–204 ng/mL; reference range: 0–100 ng/mL). The mean tumor diameter was 13 mm (range: 8–19 mm).

All patients underwent EUS-FNA biopsy for pathological confirmation. Direct smear preparations showed variable cellularity without evidence of mitosis or necrosis. Noticeable anisonucleosis was detected in one patient, which was subsequently classified as Grade 2. Cell blocks were prepared for all patients, and immunohistochemical staining demonstrated diffuse and strong cytoplasmic positivity for neuroendocrine markers. Although grading is generally discouraged in cytological specimens due to limited cell counts, Ki-67 immunohistochemical staining was performed in all patients given its role in guiding clinical management (Fig. 2). The mean Ki-67 index was 2% (range: 1–5%). Eight tumors were classified as Grade 1 and one as Grade 2. Pathological characteristics are summarized in Table 2.

Table 2
Clinical outcomes and follow-up data.

Outcome	Non-operative (n = 9)	Surgical Resection (n = 10)
Median follow-up duration, months (range)	47 (24–87)	107 (24–223)
Tumor progression	None	NA
Local recurrence	NA	None
Distant metastasis during follow-up	None	None
Postoperative complications	NA	4
– Pancreatic fistula (Grade B/C)	NA	2
– Intra-abdominal abscess	NA	1
– Delayed gastric emptying	NA	1
Median hospital stay, days (range)	NA	13 (4–39)

During mean follow-up of 47 months (range: 24–87 months), no tumor progression, NSE elevation, lymph node involvement, or distant metastasis was observed in any patient.

Surgical resection group:

Among 48 patients who underwent surgical resection during the study period, 10 met the inclusion criteria for the study. This group included five female and five male patients, with a median age of 50 years (range: 29–68) (Table 1). Diagnosis was incidental in three patients during evaluations for unrelated conditions, while seven patients had presented with mild abdominal pain. Preoperative imaging consisted of CT in nine patients and MRI in eight patients. Tumors were located in the pancreatic head (n = 4) and body (n = 6), with a mean diameter of 15 mm (range: 10–20 mm). None of the patients exhibited lymph node involvement or metastasis at diagnosis and none had pancreatic duct dilatation or peripancreatic infiltration findings.

Functional imaging was performed in seven patients: two underwent F-18 DOPA PET, which showed no significant uptake, while five underwent Ga-68 PET scans, all demonstrating functional uptake. NSE levels were available for five patients (mean: 13 ng/mL), and chromogranin A was measured in one patient (50 ng/mL).

Surgical procedures included distal pancreatectomy in six patients and pancreatoduodenectomy (Whipple’s procedure) in four patients. The mean pathological tumor size was 14 mm (range: 8–20 mm). All surgical margins were negative, and no

lymph node involvement was detected. Pathological analysis revealed two Grade 1 and eight Grade 2 tumors, with a mean Ki-67 index of 3% (range: 1–5%) (Fig. 3). Angiolymphatic invasion was observed in three cases, while no perineural invasion was reported. These findings are detailed in Table 2.

Postoperative complications occurred in three patients, all of whom had undergone distal pancreatectomy. Two of them developed postoperative pancreatic fistulas (POPF). In the first patient, POPF developed on postoperative day 4, with an initial drain output of approximately 200 mL/day. Although the drainage volume decreased to 25 mL/day by day 24, persistent elevation of inflammatory markers prompted further imaging, which revealed an intra-abdominal abscess. Percutaneous drainage was performed. Five days later, a thoracic and abdominal CT scan, performed due to recurrent fever, identified a left-sided thoracic empyema. The patient underwent thoracotomy and empyema drainage. Postoperatively, the drains were removed and the patient was discharged well 10 days after the second operation. The second patient with POPF had an initial drain output of 100 mL/day, which gradually decreased and resolved without further intervention. The patient was discharged on postoperative day 11. An intraabdominal abscess was identified on the eighth postoperative day in the third patient after developing fever the same day. Imaging revealed an intra-abdominal abscess not amenable to percutaneous drainage. Broad-spectrum antibiotic therapy was initiated. This patient also developed delayed gastric emptying which resolved with restriction of oral intake and she was discharged on day 22. The mean postoperative hospital stay in the surgical cohort was 13 days (range: 4–39 days). Postoperative outcomes and complications are summarized in Table 2.

Four patients received postoperative somatostatin analog therapy (Octreotide LAR or Lanreotide); one of them continued long-term for four years, while the others received it for one or two years. The remaining six patients did not receive adjuvant therapy. Over a mean follow-up period of 107 months (range: 24–223 months), all patients remained disease-free. One patient developed insulin-dependent diabetes mellitus during long-term follow-up.

DISCUSSION

Pancreatic neuroendocrine tumors (p-NET) are rare neoplasms, with an estimated incidence of approximately 1 case per 100,000 individuals; however, their detection has increased significantly over the past three decades, largely due to advances in imaging techniques and heightened clinical awareness [2]. This rise is particularly notable for small, asymptomatic lesions, which are frequently discovered incidentally during abdominal imaging performed for unrelated indications [14]. Recent studies advocate a multimodal management approach and highlight tumor size as a pivotal factor in decision-making, particularly for Grade 1 and 2 tumors. Accordingly, both the European

Neuroendocrine Tumor Society (ENETS) and the American Joint Committee on Cancer (AJCC) TNM classification systems base T-staging primarily on tumor diameter [15, 16]. While surgical resection has historically been the standard of care, p-NETs smaller than 2 cm are generally indolent, with reported rates of lymph node involvement or distant metastasis being low, as supported by recent prospective studies [17, 18]. This has led to increasing support for a "watch-and-wait" or active surveillance (AS) strategy in selected cases [19]. Nonetheless, tumor size alone should not be the sole criterion in determining suitability for AS in non-functional p-NET. The presence of clinical symptoms at the time of diagnosis is a key marker of biological aggressiveness. Supporting this, Sallinen et al. reported significantly worse survival outcomes in patients with symptomatic non-functional p-NET ≤ 2 cm when compared to those diagnosed incidentally [20]. In our own clinical experience, none of the patients selected for active surveillance were symptomatic at presentation. Conversely, 7 of the 10 patients who underwent surgical resection had their tumors identified during work-up for abdominal pain.

Tumor grade is a pivotal determinant of prognosis in p-NETs [21, 22]. Grade 3 tumors, regardless of size are considered to have malignant potential and should be managed accordingly [23]. Yet, the reliability of preoperative grading, especially in lesions < 2 cm, remains debatable. A study by Partelli et al. revealed that three out of four preoperatively classified Grade 2 non-functional p-NETs < 2 cm were ultimately downgraded to Grade 1 upon final pathology [24]. Similarly, in our series, a patient diagnosed with 1.5 cm Grade 2 p-NET and followed for 24 months exhibited no increase in tumor size or the emergence of any new pathological findings.

Radiological features indicative of malignancy—such as bile duct or main pancreatic duct (MPD) dilatation, lymph node involvement, distant metastases, or invasion of adjacent organs—must be meticulously assessed in the management of non-functional pancreatic neuroendocrine tumors. In particular, MPD dilatation has been increasingly recognized as a significant marker of malignant potential, even in small, asymptomatic tumors. Several studies have highlighted this association; for instance, a retrospective analysis of patients who underwent surgery for small, asymptomatic non-functional p-NET found a clear correlation between MPD dilatation and the presence of malignant features in final histopathological examination [20, 24]. Supporting these findings, a multicenter study evaluating 202 patients with non-functional p-NET ≤ 2 cm demonstrated that both MPD and bile duct dilatation were independently associated with a higher risk of disease recurrence following surgical resection [25]. Consequently, current evidence supports the consideration of active surveillance (AS) only in carefully selected patients—specifically those with incidentally discovered, asymptomatic non-functional p-NET ≤ 2 cm who exhibit no radiological features suggestive of malignancy, such as ductal dilatation.

In our series, we retrospectively analyzed a cohort consisting of 9 patients managed with active surveillance—including one patient with a grade 2 tumor—and 10 patients who underwent surgical resection. None of the patients in either group had radiological evidence of MPD dilatation or any other imaging findings indicative of malignant behavior. These results further support the notion that the absence of radiological malignancy markers, particularly MPD dilatation, may serve as a reliable criterion in selecting appropriate candidates for non-operative management.

However, optimal patient selection remains critical for the success of non-surgical strategies. Tumor size, grade, Ki-67 index and absence of lymph node involvement or distant metastasis are key parameters that should guide decision-making. Accordingly, current ENETS guidelines emphasize the importance of regular imaging and biomarker monitoring in patients under observation [15].

The parallel outcomes between both treatment groups suggest that surgical intervention may not offer additional benefit in carefully selected patients. Given the significant morbidity and potential long-term consequences associated with pancreatic surgery—even in high-volume centers—our results support a conservative, individualized approach for managing low-grade, small p-NETs. In this context, non-surgical management appears to be a safe and effective option for tumors < 2 cm in size, classified as Grade 1 or 2, and lacking lymph node involvement or metastasis. This approach also avoids the risks of surgery, including reported rates of up to 10% mortality and 40% morbidity [26, 27, 28].

In conclusion, our findings reinforce the viability of non-operative management as a safe and efficient alternative to surgical intervention in selected patients with small non-functional p-NETs.

Declarations

Consent to Participate:

The requirement for individual informed consent was waived due to the retrospective nature of the study.

Financial Disclosure

There is no financial relationship relevant to this article to disclosure.

Clinical Trial Number

Not applicable.

Conflict of Interest:

The authors declare that they have no conflict of interest.

Funding Source:

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Author Contribution

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

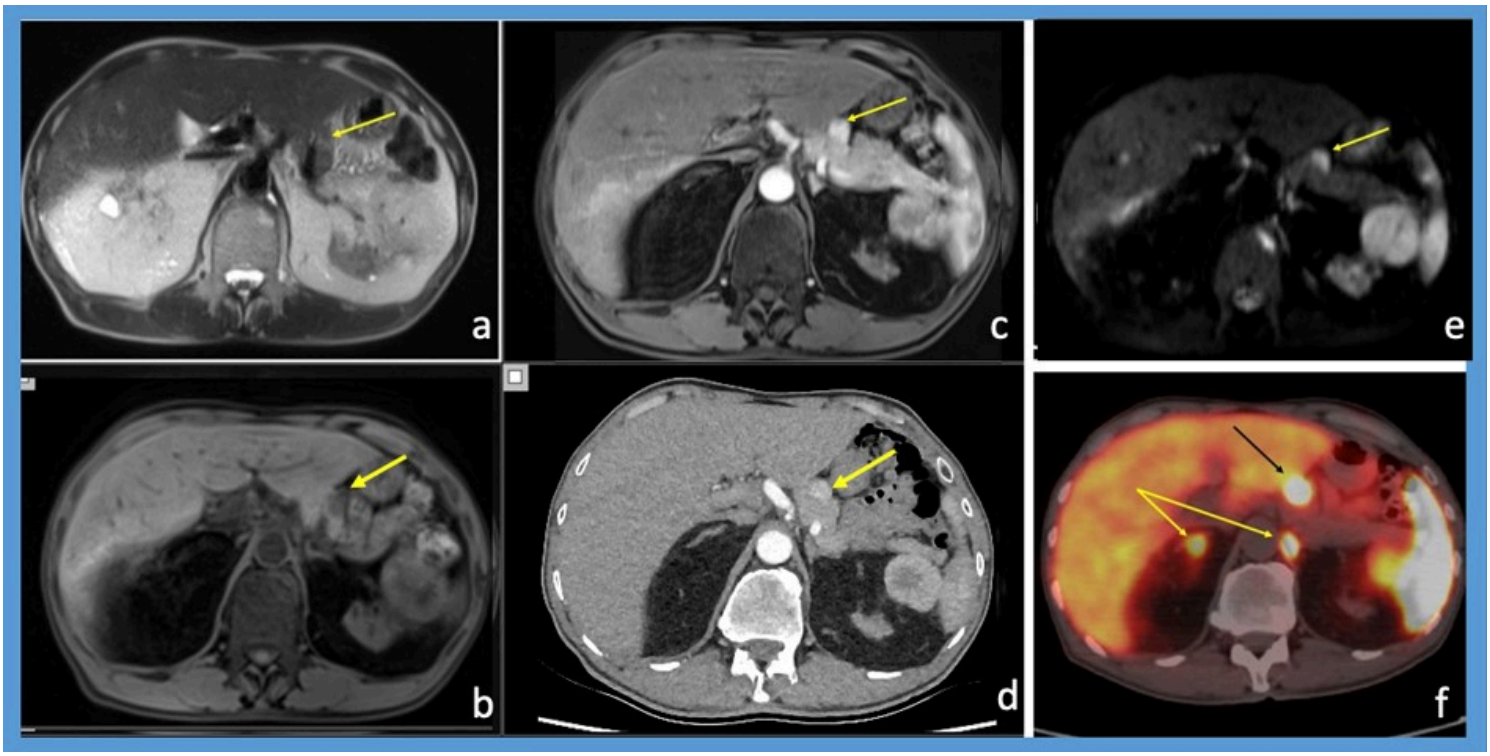


Figure 1

Radiologic evaluation of a 13×9 mm non-functioning pNET.

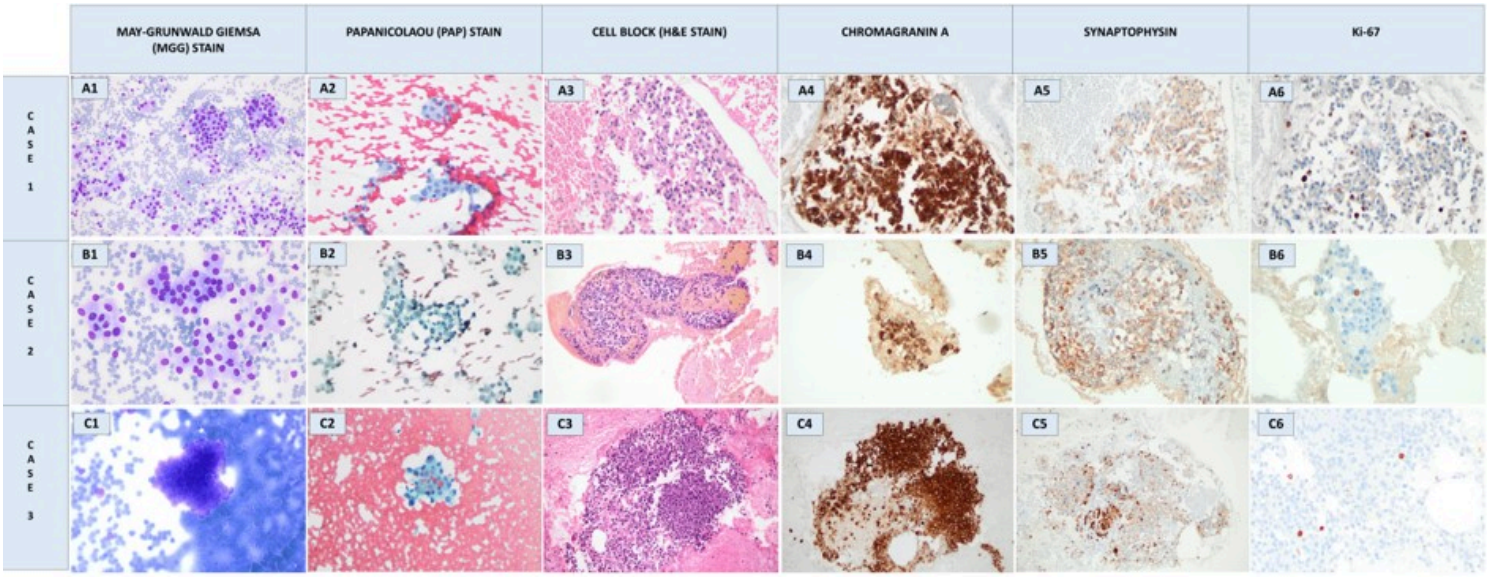


Figure 2

Cytologic and cell-block features of well-differentiated pNETs.

A- Case 1: Fine needle aspiration of a well differentiated neuroendocrine neoplasm, Grade 2. A1, A2: Direct smear; cellular smears with clusters and scattered neoplastic cells on a clean background. Tumor cells have noticeable anisonucleosis (MGG, x200), (PAP, x400), A3-A6: Cell block (H&E, x400), diffuse and strong positivity with neuroendocrine markers (chromagranin A, x400, synaptophysin, x400, Ki67; 6%, x400).

B- Case 2: Fine needle aspiration of a well differentiated neuroendocrine tumor, Grade 1. B1, B2: Direct smear; tumor cells have uniform, round to oval nuclei with salt-and-pepper chromatin and finely granular cytoplasm (MGG, x400 and PAP, x400), B3-B6: Cell block (H&E x400, chromagranin A x200, synaptophysin x400, and Ki67; 1% x400).

C- Case 3: Fine needle aspiration of a well differentiated neuroendocrine tumor, Grade 1. C1, C2: Direct smear; a cluster of neoplastic cells displays central, uniform, round nuclei with scanty cytoplasm (MGG, x400 and PAP, x400), C3-C6: Cell block (H&E x200, chromagranin A x200, synaptophysin x200, and Ki67; 2% x400).

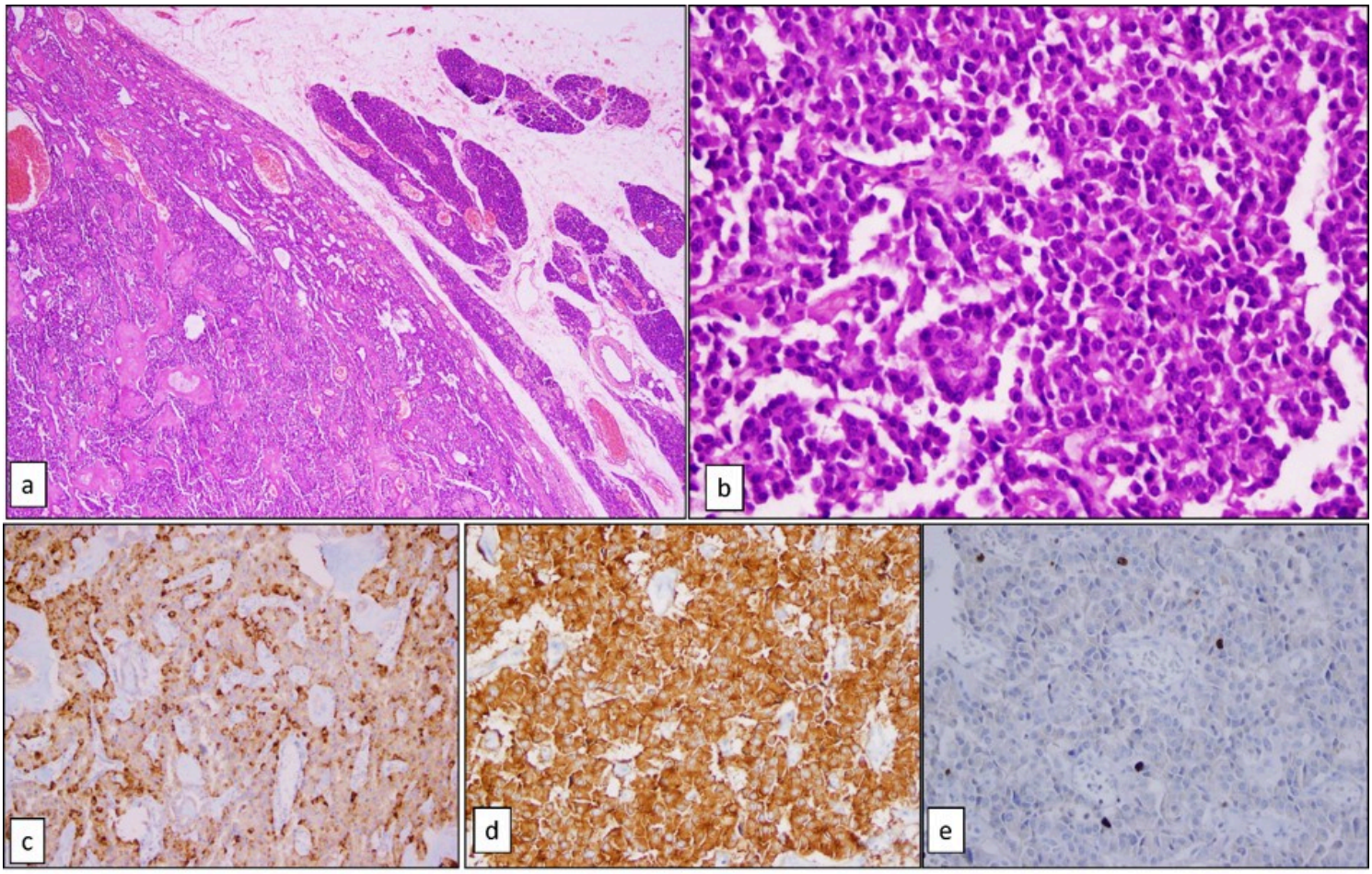


Figure 3

Histopathologic features of a well-differentiated pNET.

A well-circumscribed mass-forming pancreatic neuroendocrine tumor (PanNET) consists of acinar and solid areas rich in thin vascular spaces is seen on the left, normal pancreatic parenchyma adjacent to the tumor on the right (a). At higher magnification, monotonous tumor cells with small nuclei and eosinophilic cytoplasm form a trabecular architecture (b). The tumor shows positive cytoplasmic immunoreactivity for chromogranin A (c) and synaptophysin (d). The Ki-67 cell proliferation index is approximately 1% in the hotspot area, consistent with WHO Grade 1 (e).