Annals of Gastroenterology (2023) **36,** 1-8

Outcome of nonfunctioning pancreatic neuroendocrine tumors after initial surveillance or surgical resection: a single-center observational study

Mariola Marx[a], Fabrice Caillol[b], Sébastien Godat[a], Flora Poizat[c], Sarra Oumrani[a], Jean-Philippe Ratone[b], Solène Hoibian[b], Yanis Dahel[b], Sandrine Oziel-Taieb[d], Patricia Niccoli[d], Jacques Ewald[e], Emmanuel Mitry[d], Marc Giovannini[b]

CHUV, Lausanne, Switzerland; Paoli-Calmettes Institute, Marseille, France

Abstract

Background Current guidelines consider observation a reasonable strategy for G1 or G2 nonfunctional pancreatic neuroendocrine tumors (nf pNETs) ≤2 cm. We aimed to characterize their natural behavior and confront the data with the outcomes of patients undergoing upfront surgery.

Methods Data from patients with histologically confirmed nf pNETs ≤2 cm, managed at a single tertiary referral center between 2002 and 2020, were retrospectively reviewed.

Results Thirty-nine patients (mean age 62.1 years, 56% male) with 43 lesions (mean size 12.7±3.9 mm; 32 grade 1 [G1] and 7 grade 2 lesions [G2]) were managed by careful surveillance. Progression was observed in 15 lesions (35%; mean follow up 47 months). Six patients (18%) underwent secondary surgery because of an increase in tumor size or dilation of the main pancreatic duct; 3 of them had lymph node metastasis in the resected specimen. Surgery was followed by pancreatic fistula in 2/6 patients, 1 of whom died. Fourteen patients (mean age 59 years, 64.3% female, mean size of lesions 11.4±3.1 mm) underwent pancreatic surgery immediately after diagnosis. The surgery-associated complication rate was 57.1% (8/14). Of the 14 patients, 13 remained recurrence free (mean follow up 67 months). Recurrent metastatic disease was observed 3 years after pancreaticoduodenectomy (R0, 15 mm G2 lesion, 0 N+/8 N) in 1 patient.

Conclusions The behavior of small nf pNETs is difficult to predict, as there is evidence for malignant behavior in a subgroup of patients, even after surgical treatment. Optimal management remains challenging, as pancreatic surgery is associated with significant morbidity.

Keywords Nonfunctional pancreatic neuroendocrine tumor, endoscopic ultrasound-guided radiofrequency ablation, pancreatic surgery

Ann Gastroenterol 2023; 36 (XX): 1-8

Conflict of Interest: Mariola Marx: Fellowship in advanced endoscopy supported by Boston Scientific. The other authors have no conflicts of interest to declare.

Correspondence to: Mariola Marx, MD, Department of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, Rue du Bugnon 44, CH-1011 Lausanne, Switzerland,
e-mail: mariola.marx@chuv.ch

Received 28 January 2023; accepted 28 September 2023; published online 30 October 2023

DOI: https://doi.org/10.20524/aog.2023.0833

Introduction

In recent years, small pancreatic neuroendocrine tumors (pNETs) have been increasingly detected by chance, partially because of the widespread use of high-resolution imaging techniques for screening programs or nonspecific abdominal symptoms. Thus, patients are often diagnosed in an early and asymptomatic disease stage, with a trend toward smaller tumor size and a lower grade of malignancy [1-3].

Between 60% and 90% of all pNETs are nonfunctioning (nf) pNETs, referring to tumors without clinical symptoms of hormonal hypersecretion. More than half of them present metastatic disease at diagnosis, and approximately 20% are locally advanced [4,5]. The 2017 WHO classification distinguishes well-differentiated NETs from poorly differentiated neuroendocrine carcinomas (NECs). According

to the Ki67 proliferation index, pNETs are further subclassified into G1 (<3%), G2 (3-20%), and G3 lesions (>20%) [6].

As surgical resection carries a high risk of morbidity and mortality, current guidelines consider observation a reasonable alternative strategy for G1 or low-grade G2 pNETs ≤2 cm [5,7]. However, this wait-and-watch strategy is controversial. Strong evidence for long-term safety is lacking, and available data seem in part inconsistent. Thus, active surveillance based on high-resolution imaging is mandatory and may be associated with considerable costs. In some retrospective studies, the risk of malignancy in small nf pNETs is estimated at 5-8% [8-10]. In contrast, a recently published review of 6 retrospective studies, including a total of 344 patients with small sporadic nf pNETs, showed that approximately one-fifth of them (pooled estimate 22%) had an increase in lesion size during follow up (range 32-45 months), while none of the patients developed metastatic disease. The rate of secondary surgery in these studies ranged between 3% and 25% [11].

The principle aim of the present work was to characterize the natural behavior of small nf pNETs under careful observation and confront the data with the results and outcomes of patients undergoing upfront surgery.

Patients and methods

Acquisition of data and patient selection

In this observational study, data of patients treated at a single tertiary referral center between November 2002 and November 2020 were retrospectively reviewed. The study was approved by our institutional ethics review board and human research committee (PNETSUIVI-IPC 2020-059). Patients' medical files were found with the help of the DIAMIC and/or the CONSOR database. DIAMIC software (INFOLOGIC-healthcare, Montréal, Canada) is used in the Department of Pathology to facilitate data processing, and patients are retrieved using the corresponding histopathological codification. The CONSOR research software was developed by *Unicancer*, pooling data of all patients treated in the *Centres de lutte contre le cancer* (CLCC), and is based on a keyword search in the electronic medical files.

All patients with asymptomatic pancreatic NETs ≤2 cm were included. Diagnosis had to be confirmed histologically after endoscopic ultrasound (EUS)-guided fine needle biopsy (FNB) or on the resected specimen after pancreatic surgery. Histological evaluation was performed according to the WHO 2017 classification, based on the Ki67 index: G1 <3%, G2 3-20%, G3 >20% [6]. Lesions only visualized by EUS, but not on computed tomography (CT) or magnetic resonance imaging (MRI), were excluded, given that the initial assessment and follow up seemed less reproducible. Patients with lymph node infiltration, locally advanced or metastatic disease at the moment of initial diagnosis were excluded, as well as patients who presented symptoms due to hormonal hypersecretion. Inherited genetic syndromes were not considered an exclusion criterion. NECs or G3 NETs (Ki67 index >20%) were excluded. The decision regarding surgical resection or nonsurgical management by careful observation has always been made within the interdisciplinary tumor board. Nevertheless, management for some patients was resumed after initial follow up in external institutions.

According to our institutional policy, resection has long been the treatment of choice for all nonmetastatic pancreatic NETs. After 2012, careful surveillance became an alternative strategy for small lesions with low histopathological grading. However, some patients underwent upfront surgery even after 2012, especially in the case of main pancreatic duct (MPD) dilation or diagnostic uncertainty. Initial diagnostic workup in these patients was mainly based on cross-sectional imaging (pancreatic contrast-enhanced CT or MRI), and about half of them had histologically confirmed diagnosis before surgery.

Follow up

Patients with a follow up time <12 months were excluded, as well as patients with life expectancy <12 months or severe comorbidities in whom regular follow up did not seem beneficial.

Based on MRI or CT scan reports, we assessed tumor size, ideally biannually during the first 2 years and every 18-24 months thereafter in cases of tumor stability. If radiological follow up was not available, we contacted the patient, their general practitioner or referring gastroenterologist to complete the missing information. A significant progression was defined as tumor growth ≥20%, and a nonsignificant progression was defined as tumor growth <20%. Variations of ≤1 mm between consecutive imaging studies were considered stable disease.

In patients for whom an initial careful watch-and-wait strategy was employed, the end of follow up was defined as the last available control by high-resolution imaging, or the time of secondary surgery. Follow-up time in patients treated by first-intention surgery was based on the last available radiological control after resection, or until the follow-up imaging showing disease recurrence.

Statistical analysis

Descriptive analyses were summarized using frequencies (percentage) for categorical variables and means with standard deviations (SD), medians, and ranges for continuous variables. The risk of progression was estimated using the Kaplan-Meier method and compared between groups using the log rank test. Time until progression was measured from the first imaging study. Patients without progression were right-censored on the day of last medical follow up. Statistical analyses were performed using R, version 4.0.3 (Vienna, Austria).

[a]Department of Gastroenterology and Hepatology, CHUV, Lausanne, Switzerland (Mariola Marx, Sébastien Godat, Sarra Oumrani); [b]Department of Gastroenterology (Fabrice Caillol, Jean-Philippe Ratone, Solène Hoibian, Yanis Dahel, Marc Giovannini); [c]Department of Pathology (Flora Poizat); [d]Department of Medical Oncology (Sandrine Oziel-Taieb, Patricia Niccoli, Emmanuel Mitry); [e]Department of Surgery (Jacques Ewald), Paoli-Calmettes Institute, Marseille, France

Results

During the observation period of 18 years, 263 patients with suspected pNETs were identified. At the moment of diagnosis, metastatic or locally advanced disease was observed in 79 and 7 patients, respectively. Eighty-one patients had lesions >2 cm, 66 of whom were treated by surgical resection, whereas 15 did not undergo surgery because of age, comorbidities or patient refusal. Ten patients were treated by EUS-guided radiofrequency ablation. Twenty-three patients had insufficient or inadequate follow up (<12 months, severe comorbidities or short life expectancy). In 10 patients, histological diagnosis was missing. Thirty-nine patients treated with the surveillance strategy were finally included, and 14 patients underwent surgery immediately after diagnosis (flowchart patient inclusion, Fig. 1).

Outcomes in patients with careful surveillance strategy

The demographic characteristics of the 39 patients in whom a careful watch-and-wait strategy was employed are outlined in Table 1. Their mean age was 62.1 years (SD 10.1; range 36-83 years); 22 (56%) of them were male, and 17 (44%) were female. Nineteen of 43 lesions (44%) were localized in the head/neck, and 24 (56%) were localized in the body/tail region of the pancreas. Twenty-six percent of all lesions were cystic (11/43). Most patients had single lesions, except for 3/39 (7.7%). Two patients were diagnosed with a hereditary syndrome (MEN1, Von Hippel Lindau), but both of them had single pancreatic lesions.

The mean lesion size at the moment of diagnosis was 12.6 mm (SD 3.9; range 5-20 mm). Ten of 43 (23%) lesions were <10 mm, and 33 (77%) were 10-20 mm. Histological analysis revealed 32 G1 tumors (82%) and 7 G2 tumors (7/39 (18%), Ki67 range: 3-7%).

At the end of radiological follow up (mean FU 47±26 months; range 12-144 months, see Table 2), the mean tumor size was 15.1 mm (±7.6; range 5-38). A slight change in size (<20%) was observed in 3 lesions (2 G1 lesions and 1 G2 lesion with a Ki67 index of 5%). Twelve patients showed a significant change in the size of the lesions. Based on EUS-FNB, 6 of them were considered G1 lesions and 6 G2 lesions (Ki67 range: 3-7%). Half of the growing lesions reached a size >2 cm by the end of follow up. Fig. 2 shows the Kaplan-Meier estimation of tumor progression in patients under surveillance. There was a significant difference according to the tumor grade: all G2 lesions progressed during follow up (P=0.0018).

As a consequence of progression in tumor size or the presence of worrisome features (main pancreatic duct dilation) during follow up, 6 patients underwent secondary pancreatic resection, as outlined in Table 3. The mean time from diagnosis until surgery was 39.5 (±27.5) months. Three patients had lymph node-positive disease on resected specimens, but lymph node metastasis was not observed in any of them on preoperative imaging studies. Bearing in mind the time gap between initial evaluation by EUS-FNB and the histopathology of the surgery specimens, we found confirmation of tumor grade in 4 patients and initial overestimation and underestimation in 1 patient. In 1 patient, an initial G2 lesion (Ki67 index 4%) was classified as a G3 lesion after surgical resection (Ki67 index 22%; 66 months of surveillance).

Pancreatic surgery was followed by severe complications in 2/6 patients (33.3%), who developed pancreatic fistula with erosion of splenic vessels. In one case, hemorrhage was treated successfully, whereas bleeding could not be stopped by means of embolization or surgery in a 58-year-old male patient who died shortly thereafter.

No disease-related death or distant metastasis was observed by the end of follow up in non-resected patients undergoing ongoing surveillance.

Outcome in patients treated by upfront surgery

Fourteen patients underwent pancreatic surgery for neuroendocrine tumors ≤2 cm between November 2002 and

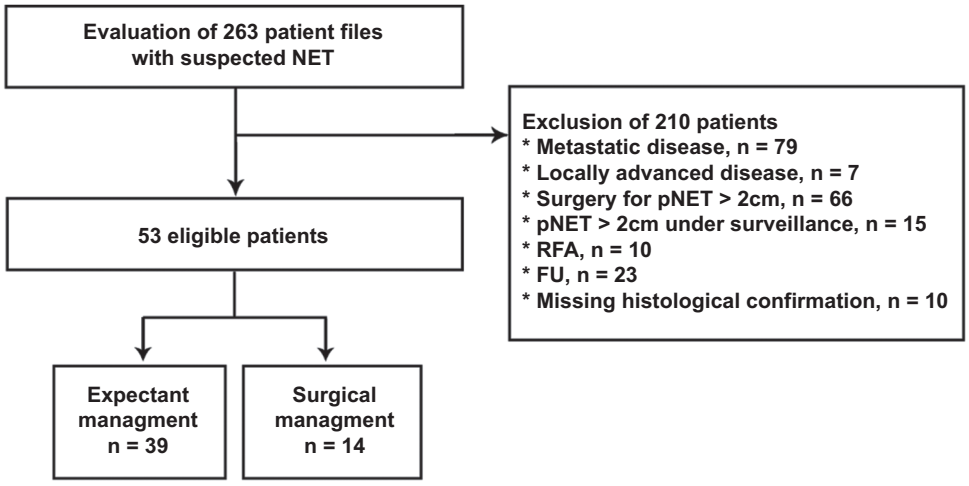

Figure 1 Flowchart patient inclusion
pNET pancreatic neuroendocrine tumor; RFA, radiofrequency ablation; FU, follow up

Table 1 Clinical characteristics at diagnosis of patients with pNET ≤2 cm and expectant management (43 lesions in 39 patients)

Characteristics	Value
Age, mean in years [SD; range]	62.1 [10.1; 36-83]
Sex	
Male, n [%]	22/39 [56]
Female, n [%]	17/39 [44]
Localization in the pancreatic gland, n	43
Head/neck, n [%]	19/43 [44]
Body/tail, n [%]	24/43 [56]
Multiple, n [%]	3/39 [7.7]
Cystic lesion, n [%]	11/43 [26]
Lesion size at diagnosis, mean in mm [SD; range]	12.6 [3.9; 5-20]
<10 mm, n [%]	10/43 [23]
10-20 mm, n [%]	33/43 [77]
Classification according to WHO 2017*	
G1 (<3%), n [%]	32/39 [82]
G2 (3-20%), n [%]	7/39 [18]
Hereditary tumor syndrome, n [%]	2/39 [5]

*assessed by endoscopic ultrasound-guided fine-needle biopsy
pNET, pancreatic neuroendocrine tumor; WHO, World Health Organization; SD, standard deviation

Table 2 Outcome of 39 patients with expectative management for 43 pNETs ≤2cm

Outcome	Value
FU, mean in months [SD, range]	47 [26; 12-144]
Lesion size at end of FU, mean in mm [SD; range]	15.1 [7.6; 5-38]
Lesions progressing during FU, n [%]	15/43 [35]
Tumor growth	
<20%, n [%]	3 [7]
Grade 1, n [%]	2 [5]
Grade 2, n [%]	1 [2]
>20%, n [%]	12 [28]
Grade 1, n [%]	6 [14]
Grade 2, n [%]	6 [14]
Patients secondarily undergoing resection, n [%]	6/39 [15]
Change in tumor size, n [%]	4 [10]
Worrisome features, n [%]	2 [5]
Lymph node metastasis on resected specimen, n [%]	3 [8]

*assessed by endoscopic ultrasound-guided fine-needle biopsy
pNET, pancreatic neuroendocrine tumor; FU, follow up; SD, standard deviation

March 2017 (Table 4; mean age 57±12.6 years, 64% (9/14) female). All patients had sporadic pNETs. The mean size of the pancreatic lesions was 10.8 mm (±3.7 mm). Five of them (36%) had worrisome features on preoperative imagery studies (dilation of the main pancreatic duct), and 1 patient underwent pancreatic resection because of diagnostic uncertainty (Table 4). The others were treated by surgery, according to the

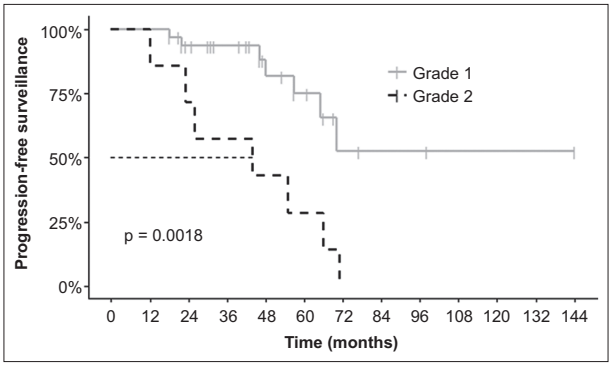

Figure 2 Progression of small pNETs under surveillance, classified as grade 1 or grade 2. Patients without progression were right-censored on the day of last medical follow up
pNET, pancreatic neuroendocrine tumor

institutional policy or patient preference. In 5 patients, caudal pancreatectomy was performed, while 3 patients underwent pancreaticoduodenectomy, median pancreatectomy or enucleation.

Preoperative EUS-FNB was performed in 5/14 patients. The Ki67 index was confirmed in 2 patients after surgery. Overestimation of the Ki67 index was observed in 1 patient, and underestimation was observed in 2 patients. In one of them, histopathological analysis of the resected specimen caused a real change in tumor grading (G1 to G2). Details are shown in Table 4. One patient had lymph node-positive disease confirmed in the resected specimen.

In patients with "worrisome features" (5/14), the post-surgical histopathological diagnosis was G1 or low grade G2 pNET without lymph-node metastasis during surgery in 80% (4/5 patients).

Eight of 14 patients (57%) suffered at least 1 postoperative complication (postoperative pancreatic fistula, n=3; collection, n=2; stenosis of the hepaticojejunal anastomosis, n=2; pleural effusions and tachyarrhythmia, n=1).

After a mean follow-up time of 69 months (range 31-153), 13/14 patients remained recurrence free. Three years after the Whipple procedure (complete resection, G2, 15 mm, 0 N+/8 N), a 64-year-old female patient developed lymph node metastasis (abdominal and mediastinal), which later progressed to liver and bone metastasis. She was treated by palliative radiochemotherapy and died 7 years after surgery.

Discussion

The decision-making process in the management of small nf pNETs remains challenging, and unequivocal criteria to predict the behavior of these tumors are still scarce. Whereas pancreatic surgery bears the risk of overtreatment in indolent neoplasms, nonoperative management by careful observation policy can miss the window of opportunity to cure potentially aggressive tumor disease.

Table 3 Secondary resection after initial surveillance in 6 patients with pNETs ≤2 cm

Patient	pNET	Surgery	Histology	Complications
	Size/grade/ localization	Indication	Grade (Ki 67) Size*	
♀, 68y	18 mm/ G2 (7%) head	PD Size 35 mm after 23 months	G2 (18%) 50 mm, 4N+/21N Duodenal infiltration	POPF with erosion of splenic vessel needing embolization
♀, 65y	12 mm/ G1 (1%) head	PD MPD dilation	G1 (Ki 1.5 %) 12 mm, 0N+/12N	Gastroparesis
♀, 52y	13 mm/ G2 (4%) tail	CP Size 30 mm after 21 months	G1 (1.5%) 20 mm 0N+/1N	none
♀, 68y	14 mm/ G2 (4%) neck	CP Size 38 mm after 66 months	G3 (22%) 40 mm 5N+/11N	none
♂, 74y	17 mm/ G2 (<5%) body	CP Size 30 mm after 55 months	G2 (3%) 25 mm 1N+/3N	none
♂, 58y	10 mm/ G1 (1%) neck	CP MDP dilation	G1 (2%) 15 mm 0N	POPF grade C Erosion of splenic vessels at day 10, death

*assessed on resected specimen

CP, caudal pancreatectomy; Dx, diagnosis; E, enucleation; EUS, endoscopic ultrasound; M, metastasis; MP, median pancreatectomy; N, lymph node; pNET, pancreatic neuroendocrine tumor; PD, pancreaticoduodenectomy; POPF, postoperative pancreatic fistula; MDP, main pancreatic duct

Several studies argue for an indolent disease course of small pNETs, suggesting that a careful "wait-and-watch strategy" seems reasonable in selected patients [12-16]. Interim analyses of the prospective PANDORA and ASPEN trials suggest that a non-operative strategy seems safe, as only a negligible fraction of patients have an increase in tumor size [17,18]. In a recent meta-analysis, 84 of 267 patients with sporadic nf pNET showed increasing tumor size (range across studies 0-51%, pooled estimate 22%), but no patients developed lymph-node or distant metastasis during follow up. The percentage of patients undergoing surgical resection after expectant management varied highly, between 3% and 25% (pooled estimate 12%) [11]. Another meta-analysis revealed 14% of patients undergoing pancreatic surgery after the initial wait-and-watch strategy, with a median time from diagnosis to surgery of 30-41 months [19].

The results of the present work suggest even higher progression rates. Accordingly, approximately one-third of all lesions were found to be growing during follow up (35%). At the end of follow up, half of the growing lesions had reached a size >2 cm. Three of these patients were secondarily treated by surgery and found to have lymph node-positive disease on resected specimens. This does not appear surprising, as tumor size is known to correlate with the probability of lymph node involvement [20].

In a retrospective study on predictors of lymph node involvement in nf pNETs, Partelli *et al* found intraoperative nodal metastases in 30% of patients, approximately half of which were not visualized on preoperative cross-sectional imaging. However, 39% of all 181 included patients turned out to have G2 lesions, and the radiological tumor size before surgery was >4 cm in 26% of patients [21]. In the present study, the rate of intraoperative discovery of lymph node disease was similar in both groups: in patients who were primarily (1/14 [7.1%] G2 lesion) resected and those who were secondarily (3/39 [7.7%], all G2 lesions) resected.

All pNETs classified as G2 in the present work (n=7; initial tumor size 12-18 mm) progressed over time. Previous studies have shown that the Ki67 index is a key prognostic factor for the disease-specific survival of patients with pNETs [20,22,23]. In contrast, in a multicenter study with 88 patients, the Ki67 index was not found to be an independent predictor of malignancy. Unfortunately, only a minor portion of the currently available studies reporting on the wait-and-watch strategy in small pNETs provide histological grading and the Ki67 index. Furthermore, precise information about the correlation between grading and progression is scarce [13-15,24]. Based on the results of the present study, a careful watch-and-wait strategy for G2 pNETS should be applied with great caution. There should be a low threshold for more invasive treatment in cases of progression during close follow up.

In addition, this preliminary study found that a considerable proportion of G1 pNETs progressed during follow up (8/43, 18.6%). Even though the difference between the mean size of all included pNETs at the beginning and at the end of follow up was only 3 mm, a total of 8 G1 lesions progressed, with a mean increase of 4.6 mm. In a matched

Table 4 Outcomes of patients treated by surgery for nf pNET ≤2 cm (n=14)

Patient	pNET	Surgery	Histology	Complications	FU	Px
	Size*/ localization	(Indication)	Grade (Ki 67) FNB/Surgery		months	
♂, 64y	12 mm, tail	CP	G2 (6%) / G2 (4%)	POPF grade B	102	no
♂, 69y	12 mm, junction body/tail	CP	- / G2 (<10%)	Collection	44	no
♀, 57y	10 mm, neck	CP	- / G1 (<1%)	Collection	85	no
♀, 52y	15 mm, tail	E	- / G2 (<5%)	no	100	no
♀, 77y	9 mm, body	MP (MDP dilation)	- / G1 (1%)	no	51	no
♀, 55y	17 mm, head	MP	G1 (2%) / G1 (2%)	POPF grade A	60	no
♀, 62y	18 mm, head	PD (MDP dilation)	G1 (2%) / G2 (<10%) 2N+/7N	Stenose of the hepatico-jejunal anastomosis with iterative cholangitis	139	no
♀, 48y	10 mm, neck	E	- / G1 (2%)	no	59	no
♀, 64y	15 mm, tail	PD (MDP dilation)	- / G2 (na) 0N+/8N	POPF grade B	36	N+M+
♀, 57y	15 mm, neck	E	G1 (<2%) / G1 (<2%)	no	153	no
♀, 71y	10 mm, tail	CP (Dx uncertain)	- / G1 (2%)	Pleural effusion, tachyarrhythmia	71	no
♂, 36y	10 mm, body	MP (MDP dilation)	G1 (1%) / G1 (2%)	no	67	no
♂, 54y	13 mm, head	PD (MDP dilation)	- / G1 (1%) 0N+/10N	Stenose of the hepatico-jejunal anastomosis with iterative cholangitis	31	no
♂, 32y	3 mm, body	CP (Progression at 6 months)	- / Grade not evaluable	no	75	no

*assessed on resected specimen

CP, caudal pancreatectomy; Dx, diagnosis; E, enucleation; EUS, endoscopic ultrasound; M, metastasis; MP, median pancreatectomy; N, lymph node; nf pNET, nonfunctioning pancreatic neuroendocrine tumor; PD, pancreaticoduodenectomy; POPF, postoperative pancreatic fistula, Px, progression; MDP, main pancreatic duct

case-control study by Sadot *et al*, 50% of observed lesions progressed, but the median tumor size had not changed at the end of follow up (1.2 cm, P=0.7). Notably, 31% of lesions showed decreasing tumor size. Similarly, in our study, 4/43 lesions regressed (n=4, mean difference in size 5.5±3.1 mm). Until the end of follow up, none of the patients with G1-pNET developed lymph node or distant metastasis, and there was no disease-related death. This is concordant with previously published data [11,14,19].

One of the patients treated with upfront surgery in this study suffered disease recurrence 3 years after R0/N0 resection of a G2 lesion. Sadot *et al* described 77 initially resected patients with pNETs <3 cm, of whom 5 (6%) had recurrent disease after a median follow up of 5.1 years. Since they found a rate of late metastasis and recurrence in 3/39 (7.7%) patients with lesions <2 cm, Haynes *et al* suggested tumor resection and careful postoperative surveillance, even in small pNETs with favorable pathological findings. However, only 1 of these 3 patients was classified as "benign", defined as well-differentiated without characteristics of malignant disease [8,14]. In the present study, 5/14 patients underwent upfront surgery because of worrisome features: almost all of them had localized G1 or low grade G2 disease in the resected specimen. In 1 patient, a known G2 lesion (EUS-FNB before surgery) was shown to have lymph-node metastasis on the resected specimen.

However, morbidity and mortality inherent to pancreatic surgery are still considerable [7,25]. In the present study, the pooled surgery-associated complication rate in patients treated by primary or secondary resection was 50%, and 1 patient died following caudal pancreatectomy. Previous studies reported comparable results. In a retrospective review of 55 patients in Tel Aviv treated by upfront surgery for mainly G1 small pNETs (48/55 lesions with Ki-67 index <3%), adverse events were reported in 51%, and 1 patient died because of a complicated pancreatic leak. Parenchymal-sparing resections are considered a reasonable treatment strategy for small low-grade malignant tumors. Nevertheless, enucleation, for instance, is associated with a high complication rate, mainly due to pancreatic fistula. It

is important to remember that the importance of regional lymphadenectomy in small pNETs remains controversial and lymph node dissection is not systematically performed [26,27]. Thus, less invasive ablation strategies, such as EUS-guided radiofrequency ablation, should present a promising alternative treatment strategy in well-defined patients. Associated adverse events are often transient in nature and can be managed noninvasively or endoscopically. Of course, long-term outcomes have to be awaited, but they might be comparable to those of surgery, especially if patients are treated at an early stage.

The patient review reported here has certain limitations that deserve discussion. The results are limited by the observational and monocentric study design, with a restricted number of patients. Thus, it was decided to present results mainly in a descriptive manner and provide detailed insight into patient outcomes. Evaluation of tumor progression is principally based on imaging reports from radiologists with experience in pancreatic disease. However, a systematic retrospective review of images was not performed. Follow ups were based on MRI or CT imaging studies, as they seemed most objective and reproducible. However, some patients with follow up by EUS or transabdominal ultrasound have been excluded, even if some recent data suggest that EUS might be the best correlating imaging tool in pNETs <20 mm [28]. Some patients who had irregular or missing external follow up by general practitioners were excluded. Patients with advanced tumor disease other than pNET were not taken into account, especially when life expectancy was significantly limited, and surveillance was focused on another predominant disease. Chromogranin A (CgA) levels were not reported in this study, as their routine use is of limited importance in cases of small NET lesions, and information about CgA was only available for a small number of the included patients. Somatostatin receptor-based imaging studies have not been performed routinely.

A strong point of this study was the histological confirmation of all lesions. Recent studies report adequate tissue sampling during EUS-FNB in 86%. Even if the high variability of Ki-67 in different areas of pNETs impedes an accurate assessment of tumor grading by EUS-fine-needle aspiration/EUS-FNB, there is some evidence that concordance between preoperative and postoperative histological analysis is acceptable, estimated at 80%. Especially for lesions <2 cm and biopsies performed in the recent era the concordance reaches >90% [29]. However, the data reported herein did not allow us to investigate the reliability of EUS-FNB, as there was a long delay between the first EUS-FNB and secondary resection in the observation group, and only a few patients in the upfront surgery group had preoperative EUS-FNB.

In conclusion, the behavior of small nf pNETs is difficult to predict, and there is growing evidence for malignant behavior in a subgroup of patients, even after surgical treatment. Optimal management remains challenging, as pancreatic surgery is associated with significant morbidity.

Summary Box

What is already known:

- Most nonfunctioning pancreatic neuroendocrine tumors (pNETs) have an indolent disease course, but criteria to predict the behavior of these tumors are still scarce
- Several studies suggest a careful "wait-and-watch-strategy", as pancreatic surgery has an appreciable morbidity rate

What the new findings are:

- One third of all small pNETs increased during follow up, and half of these growing lesions reached a size >2 cm
- All G2 pNETs included in this study progressed in size, a careful watch-and-wait strategy for these lesions should be applied with great caution
- There should be a low threshold for more invasive treatment in cases of progression during close follow up

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