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Management of small asymptomatic nonfunctioning pancreatic neuroendocrine tumors: Limitations to apply guidelines into real life

Stefano Partelli, MD, PhD[a,b], Michele Mazza, MD[a], Valentina Andreasi, MD[b], Francesca Muffatti, MD[b], Stefano Crippa, MD, PhD[a,b], Domenico Tamburrino, MD[a], Massimo Falconi, MD[a,b,*]

[a] Pancreatic Surgery Unit, Pancreas Translational & Clinical Research Center, San Raffaele Scientific Institute, Milan, Italy
[b] Vita e Salute University, Milan, Italy

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ABSTRACT

Background: International guidelines suggest a watchful strategy for small nonfunctioning pancreatic neuroendocrine tumors. The aim of this study was to evaluate the management and indications for surgery in patients with asymptomatic nonfunctioning pancreatic neuroendocrine tumors ≤2 cm.
Methods: Patients with asymptomatic, incidental, sporadic nonfunctioning pancreatic neuroendocrine tumors ≤2 cm without nodal or distant metastases were included (2012–2016). A comparison between active surveillance and surgery groups was performed.
Results: Of the 101 included patients, 72% underwent active surveillanc and 28% were surgically treated. Patients submitted to surgery were significantly younger (53 vs 60 years, $P = .013$), had a higher incidence of positive ^{18}F-fluorodeoxyglucose positron emission tomography (18% vs 50%, $P = .003$), and a higher incidence of cytologically determined G2 tumor (0% vs 14%, $P = .008$). Conservatively managed patients had a significantly smaller tumor size (12 vs 16 mm, $P = .0001$). The main reasons determining surgical choice were as follows: patient's preference (32%), positive ^{18}F-fluorodeoxyglucose positron emission tomography (21.5%), main pancreatic duct dilation (17.5%), cytologically determined G2 tumor (14.5%), and young age (14.5%). At a median follow-up of 40 months, all of the 73 patients conservatively managed were alive, with no evidence of distant metastases and none underwent surgery. Only 5 patients had a tumor growth >20%.
Conclusion: One-third of patients with asymptomatic small nonfunctioning pancreatic neuroendocrine tumors ≤2 cm underwent surgery. Patient's preference, initial tumor size, and young age were the main determinants of surgical indication. Preoperative diagnostic workup, including ^{18}F-fluorodeoxyglucose positron emission tomography and cytologic grading, seems to be poorly accurate in determining malignant features in these small lesions.

Background

Pancreatic neuroendocrine tumors (PanNETs) are rare neoplasms representing the 1% to 2% of all pancreatic tumors.[1,2] Despite their rarity, the incidence of PanNETs has steadily risen in the past decade, from 0.4 to 0.8 per 100,000 inhabitants.[3] This growth of incidence is mainly attributable to the increasing number of small sporadic incidentalomas, as shown in a recent retrospective population analysis that reported a doubling of the proportion of PanNETs ≤2 cm during the past 22 years.[4] This rise could for the most part be related to the widespread use of cross-sectional imaging, which brought an overdiagnosis of small, asymptomatic and nonfunctioning PanNETs (NF-PanNETs). It has been shown that most of NF-PanNETs ≤2 cm are likely to be benign lesions, with a low tendency to progression when incidentally discovered.[5–7] As a consequence, considering the high morbidity and the long-term functional impairment after pancreatic resections, a routine surgical indication for these small lesions has been challenged.[8] Several series have demonstrated the feasibility and the safety of an active surveillance management for NF-PanNETs with a

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Stefano Partelli and Michele Mazza share first authorship.
* Reprint requests: Massimo Falconi, MD, Pancreatic Surgery Unit, Pancreas Translational & Clinical Research Center, San Raffaele Scientific Institute, "Vita-Salute" University, Via Olgettina 60, 20132 Milan, Italy.
E-mail address: falconi.massimo@hsr.it (M. Falconi).

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maximum diameter ≤2 cm.[6,8–13] Consequently, in these cases a watchful strategy has been suggested by the European Neuroendocrine Tumor Society (ENETS)[14,15] and by the National Comprehensive Cancer Network.[16]

Nevertheless, these guidelines suggested weighing the risk–benefit ratio of a surgical approach of NF-PanNET ≤2 cm, but no recommendations were provided regarding initial diagnostic assessment and how to deal with challenging situations. In particular, it may be difficult to manage these small lesions when they occur in young patients or when they are associated with preoperative radiologic or histologic worrisome features.

Moreover, several issues need still to be addressed to overcome some skepticism concerning this conservative attitude.[17–19] In particular, data regarding the natural history and the long-term evolution of these lesions are still lacking, with no recognized features that can predict a malignant behavior. Hence, it is unclear whether a conservative approach can be offered to all patients and whether it can be adequately implemented.

The primary outcome of the present study was the evaluation of the management and indications for surgery in patients with asymptomatic NF-PanNETs ≤2 cm. The secondary outcomes were to analyze the value of the findings obtained by an extensive initial diagnostic workup and to evaluate the tumor growth during the follow-up period among patients who underwent active surveillance.

Methods

Study design

The present study was a retrospective cohort study and was conducted at San Raffaele Scientific Institute, Milan, Italy following the STrengthening the Reporting of OBservational studies in Epidemiology statement (STROBE) guidelines.[20] All the patients diagnosed with NF-PanNET from January 2012 to December 2016 were retrospectively screened. Inclusion criteria were as follows: age ≥18 years, diagnosis of NF-PanNET proven with either a positive fine needle aspiration (FNA) obtained by endoscopic ultrasound (EUS) or with a positive ^{68}Gallium (^{68}Ga) positron emission tomography (PET), absence of tumor-related symptoms, radiologic tumor size ≤2 cm, and absence of nodal or distant metastasis after the diagnostic workup. Patients with functioning forms were excluded, as were those with inherited syndromes.

Definitions of outcomes

The management of patients with an incidental diagnosis of NF-PanNET ≤2 cm was based on the ENETS guidelines,[14,15] although several criteria were also considered. A specific protocol was not adopted but, generally, the presence of the following criteria was defined as mandatory indications for surgical intervention in patients deemed fit for surgery: tumor growth more than 2 cm during follow-up, occurence of symptoms directly related to the neoplasms, radiologic evidence of main pancreatic duct (MPD) dilatation, lymph nodes enlargement, nearby organs or main peripancreatic vessels infiltration, a strong ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) positivity, and age <50 years. Relative indications for surgery included a weak ^{18}F-FDG PET positivity, a tumor size >1.5 cm, and age >50 years and ≤70 years. In the presence of relative indications for surgery, risks and benefits of a pancreatic resection were carefully weighed, with the patients who were eventually operated on or not, according to their preferences. Initial diagnostic workup always included at least one high-quality imaging examination (computed tomography [CT] or magnetic resonance imaging [MRI]), and it was always completed either with ^{68}Ga PET or EUS with FNA. Combined ^{18}F-FDG and ^{68}Ga/PET was routinely performed except for those patients who were referred to our institution having already had a ^{68}Ga PET. Also EUS with FNA was not repeated in those patients who had a prior cytologic diagnosis.

A standard pancreatic resection (pancreaticoduodenectomy or distal pancreatectomy) was routinely proposed in the presence of a dilated MPD or when nearby structures were involved. In the remaining cases, the feasibility of an atypical resection (enucleation or middle pancreatectomy) was routinely evaluated because of the negligible risk of nodal metastases in NF-PanNET ≤2 cm. Enucleation was also excluded when the lesion appeared to be located <3 mm from the MPD.[21] In the case of atypical resection (enucleation or middle pancreatectomy), nodal sampling was only performed in the presence of suspected lymph nodes. A minimally invasive approach, including laparoscopic distal pancreatectomy and laparoscopic enucleation, was progressively implemented beginning in 2014.

In the active surveillance group, patients were monitored with a follow-up schedule consisting of an MRI or a CT every 12 months alternated with an abdominal ultrasound (US) every 6 months. If no tumor progression was detected in the first 2 years, only a CT or an MRI was then performed on a yearly basis.

Data collection

Demographic variables, clinical presentation, radiologic features, perioperative and pathologic variables, and follow-up records were retrospectively reviewed from an electronic database. At the final histology, tumors were classified according to the current ENETS tumor node metastasis classification.[22] The status of surgical margins was classified into the following: R0 (no residual tumor) and R1 (microscopic residual tumor). The Ki67 index was assessed in the surgical specimen by MIB1 antibody staining and evaluated by measuring the percentage of cells with positive nuclear staining after the count of 2,000 cells in the area of the highest nuclear labelling.[23] Tumor grade was classified according to the latest World Health Organization classification into two categories: NF-PanNET G1 (Ki67 < 3%) and NF-PanNET G2 (Ki67 3%–20%).[23] None of the patients had a diagnosis of NF-PanNET G3 or NF-PanNEC G3. The Clavien-Dindo grading system was used to assess the severity of postoperative complications.[24] Pancreatic fistula, postoperative haemorrhage, and delayed gastric emptying were defined following the International Study Group on Pancreatic Surgery classifications.[25–27] For both groups, the follow-up was updated with routine clinical visits and high-quality imaging (usually MR) a minimum of every 12 months, irrespective of pathologic findings in the surgical group. Endocrine and exocrine pancreatic insufficiency were respectively defined as the appearance or worsening of postoperative diabetes and the requirement of pancreatic enzyme supplementation therapy to relieve maldigestion-related symptoms.

Statistical analysis

Continuous data were reported as median and interquartile range (IQR). Categorical data, number, and percentage (%) were displayed. The study population was divided in two groups, including patients submitted to active surveillance or surgery, respectively. The comparison between the two groups was performed using the Mann-Whitney *U* test for continuous variables. Qualitative data were compared by the χ^2 test or the Fisher exact test, when appropriate. Multiple logistic regression analysis was used to identify the independent predictors of surgical management. Statistical analyses were performed in SPSS 25.0 for Mac

Table I
Comparison of demographic, clinical, and radiological characteristics between patients diagnosed with nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs) ≤2 cm who underwent active surveillance and those submitted to surgery

Variable	Active surveillance n = 73 (%)	Surgery n = 28 (%)	Overall n = 101 (%)	*P* value
Sex				
Male	36 (49)	10 (36)	46 (45.5)	
Female	37 (51)	18 (64)	55 (54.5)	.268
Age, years*	61 (52.5; 71)	53.5 (41.5; 66)	59 (49; 69)	**.013**
Incidental diagnosis				
Nonspecific symptoms	30 (41)	14 (50)	44 (43.5)	
Follow-up of other diseases	26 (36)	11 (39)	37 (36.6)	.480
Other causes†	17 (23)	3 (11)	20 (19.8)	
Largest radiologic diameter, mm*	12 (10;15)	16 (14;20)	13 (10;16)	**< .0001**
First-line imaging				
Transabdominal ultrasound	38 (52)	14 (50)	52 (51.4)	
Computed tomography	23 (32)	8 (29)	31 (30.7)	
Magnetic resonance imaging	9 (12)	6 (21)	15 (14.8)	.712
Endoscopic ultrasound	3 (4)	0 (0)	3 (2.9)	
Location in the pancreas				
Head	29 (40)	11 (39)	40 (39.6)	
Body	31 (42)	10 (36)	41 (40.6)	
Tail	10 (14)	7 (25)	17 (16.9)	.503
Multifocal	3 (4)	0 (0)	3 (2.9)	
Lesion morphology				
Solid	65 (89)	25 (89)	90 (89.2)	
Cystic	6 (8)	1 (4)	7 (6.9)	.484
Solid cystic	2 (3)	2 (7)	4 (3.9)	
MPD dilatation				
No	73 (100)	22 (79)	95 (94.1)	
Yes	0 (0)	6 (21)	6 (5.9)	**< .0001**
Follow-up from diagnosis, months*	40 (23;52)	37 (27;59)	38 (25;52)	.601

* Expressed as median (interquartile range [IQR]).
† Severe episode of diarrhea, renal lithiasis, hypertransaminasemia, thrombophlebitis, GGT increase, syncope, and cutaneous rash.

software (SPSS Inc, Chicago, IL, USA). *P* values ≤.05 were considered significant.

Results

Management of patients with incidental NF-PanNETs ≤2 cm

Overall, 101 patients diagnosed with NF-PanNETs ≤2 cm were included in the study. Among these, 73 patients (72%) underwent active surveillanc, whereas in the remaining 28 cases (28%) an upfront pancreatic resection was performed.

A comparison of demographic, clinical, and radiologic characteristics is reported in Table I. Patients undergoing pancreatic resection were significantly younger than those conservatively managed (median 53.5 years [IQR 41.5; 66 years] vs 61 years [IQR 52.5; 71 years], $P = .013$). Patients who were conservatively managed had a significantly smaller tumor size compared with those surgically treated (median 12 mm [10; 15 mm] vs 16 mm [14; 20 mm], $P = .0001$). A dilatation of the MPD was observed in 6 cases, all belonging to the surgery group ($P = .001$). On multivariate analysis, factors independently associated with the risk of undergoing surgery were the radiologic diameter (odds ratio [OR]: 0.942, confidence interval [CI]: 0.899; 0.968, $P = .01$) and the age at the time of diagnosis (OR: 1.306, CI 1.106; 1.543, $P = .002$).

Prognostic implications of initial diagnostic workup

A positive ^{18}F-FDG PET was significantly more frequent in patients treated with an operative management ($P = .003$; Table II). All patients ($n = 4$) with a cytologically determined G2 tumor underwent surgery ($P = .008$), and among these 4 patients, only 1 had a G2 neoplasm confirmed at the final histology on surgical specimen. The remaining 3 patients were downgraded to G1.

The reasons determining the surgical management were patients' preferences ($n = 9$, 32%), the presence of strong positivity at ^{18}F-FDG PET ($n = 6$, 21.5%), the presence of MPD dilatation ($n = 5$, 17.5%), a cytologically determined G2 tumor ($n = 4$, 14.5%; Ki67 range 4%–8%), and a young age (36–41 years, $n = 4$, 14.5%). In the surgical group, the preoperative diagnosis of NF-PanNET was obtained only by a combination of morphologic and functional imaging (^{68}Ga PET positivity) in 7 patients. In these 7 patients, a definitive cytologic diagnosis was not possible in 6 patients. In 1 patient, the FNA revealed a suspected pancreatic cancer not confirmed by the final histologic report. Perioperative details and pathologic features of patients who underwent surgery are summarized in Tables III and IV. Malignant pathologic features were found only in 3 patients after surgery. Nodal metastases were reported in only 2 patients. Both of them also had an NF-PanNET-G2 with microvascular and perineural invasion and associated MPD dilatation that was detected preoperatively. Microvascular invasion was found also in another patient who underwent surgery, with the presence of a positive ^{18}F-FDG PET (SUV = 17). Among the cases with a positive ^{18}F-FDG PET ($n = 14$), only 5 had at least 1 pathologic feature of aggressiveness, such as a G2 tumor ($n = 5$), microvascular invasion ($n = 3$), perineural invasion ($n = 1$), or nodal metastasis ($n = 1$).

Surgery and active surveillance outcomes

Among 28 patients who underwent upfront surgery, severe post-operative complications (Clavien-Dindo = III) occurred in 5 patients (24%), with no reported surgery-related mortality. The most frequent complication was postoperative significant

Table II
Comparison of diagnostic findings between patients diagnosed with nonfunctioning pancreatic neuroendocrine tumors (NF-PanNET) ≤2 cm who underwent active surveillance and those submitted to surgery

Variable	Active surveillance n = 73 (%)	Surgery n = 28 (%)	*P* value
68-Gallium PET			
Negative	5 (7)	2 (7)	
Positive	46 (63)	17 (60)	1.000
Not performed	22 (30)	9 (32)	
18F-FDG PET			
Negative	16 (22)	2 (7)	
Positive	13 (18)	14 (50)	**.003**
Not performed	44 (60)	12 (43)	
FNA			
Diagnostic for NET	35 (48)	12 (43)	
Undetermined/misdiagnosed	9 (12)	7 (25)	.329
Not performed	29 (40)	9 (32)	
Cytologic grading[23]			
G1	20 (27)	5 (18)	
G2	0 (0)	4 (14)	**.008**
Not performed	53 (73)	19 (68)	

Table III
Postoperative outcomes characteristics of patients diagnosed with nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs) ≤ 2 cm who underwent surgery (*n* = 28)

Variable	*n* (%)
Surgical procedure	
Pancreaticoduodenectomy	5 (18)
Distal pancreatectomy	12 (42)
Open*	8 (67)
Laparoscopic*	4 (33)
Enucleation	10 (36)
Open†	7 (70)
Laparoscopic†	3 (30)
Middle pancreatectomy	1 (4)
Complication severity[24]	
Grade I–Grade II	16 (76)
Grade III	5 (24)
Surgical complication	
Pancreatic fistula[25]	17 (61)
Biochemical leak	10
Grade B	7
PPH grade A[26]	1 (3.5)
DGE syndrome grade A[27]	2 (7)
Chile leak	3 (10.5)
Abdominal fluid collection	7 (25)
Length of hospital stay, days‡	9 (7; 10)
Readmission	
No	20 (71)
Yes	8 (29)
Exocrine pancreatic insufficiency	
No	20 (71)
Yes	8 (29)
Endocrine pancreatic insufficiency	
No	25 (89)
Yes	3 (11)

PPH, postoperative haemorrhage; *DGE*, delayed gastric emptying.
* Percentage calculated on patients who underwent distal pacreatomy.
† Percentage calculated on patients who underwent enucleation.
‡ Expressed as median (interquartile range [IQR]).

Table IV
Pathologic outcomes diagnosed with nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs) ≤2 cm who underwent surgery (*n* = 28)

Variable	n (%)
PanNET largest diameter, mm*	15.5 (14; 20)
PanNET grade[23]	
G1	22 (79)
G2	6 (21)
T stage[22]	
T1	26 (93)
T2	2 (7)
N stage[22]	
Nx	6 (21)
N0	20 (72)
N1	2 (8)
Resection margin	
R0	28 (100)
R1	0 (0)
Microvascular invasion	
No	25 (89)
Yes	3 (11)
Perineural invasion	
No	26 (93)
Yes	2 (7)
Necrosis	
No	28 (100)
Yes	0 (0)

* Expressed as median (interquartile range [IQR]).

pancreatic fistula (*n* = 7, 25%). At a median follow-up of 37 months (IQR 27; 59 months), no patients developed local recurrence or distant metastases after surgery. After a median follow-up of 40 months (IQR 23; 52 months), in the 73 patients who underwent active surveillance, no distant metastases or nodal metastases occurred. No patients underwent surgery during follow-up, and only 1 patient died for reasons unrelated to the presence of NF-PanNET. The NF-PanNET growth characteristics are summarized in Table V. In most of the subjects, the tumor radiologic diameter remained either stable (*n* = 55, 75%) or had a limited growth <20% (*n* = 13, 18%). Only in 5 cases (7%), tumor diameter increased more than 20% (Figure). Only 2 cases (1 with a tumor growth <20% and 1 with a tumor growth ≥20%) had a final tumor diameter greater than 20 mm, but surgical treatment was not offered to them because of the presence of relevant comorbidities and advanced age. The remaining 4 patients with a tumor diameter increase of ≥20% had a final tumor size between 14 mm and 19 mm, and they are still continuing active surveillance. Median tumor radiologic diameter at the last follow-up was 13 mm (IQR 10; 15.5 mm) compared with 12 mm (IQR 10; 15 mm) at baseline (*P* < .0001).

Discussion

In the present study the majority of patients affected by asymptomatic NF-PanNETs ≤2 cm were safely observed, although a

Table V
Characteristics of nonfunctioning pancreatic neuroendocrine tumor (NF-PanNET) growth over follow-up time in 73 patients who underwent active surveillance

Variable	Median (IQR)
Largest radiologic diameter, mm*	
Baseline	12 (10; 15)
Follow-up	13 (10; 15.5)
Tumor growth†	
No tumor growth	55 (75)
<20%	13 (18)
≥20%	5 (7)
Follow-up, months	40 (23; 52)
Overall tumor growth‡	
mm	1 (1; 4)
%	10.5 (7.4; 35.4)
Tumor growth per year‡	
mm	0.6 (0.3; 1)
%	4.6 (2.8; 9.2)

* $P < .0001$.
† Expressed as number (%).
‡ Calculated on patients who had tumor growth.

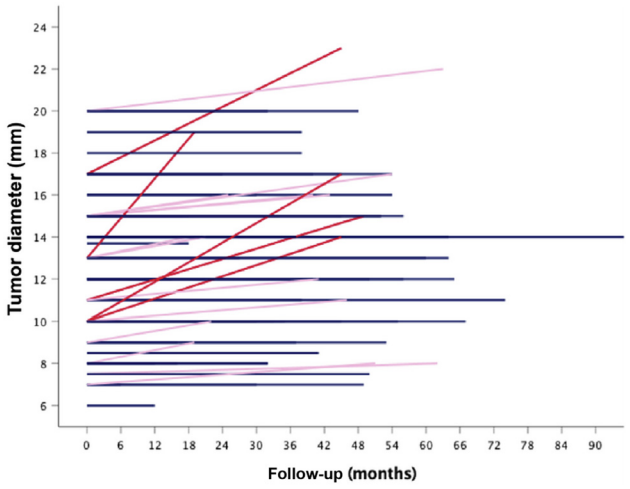

Figure. Nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs) growth over follow-up time in 73 patients who underwent active surveillance (*blue*: no growth, *pink*: growth <20%, *red*: growth ≥20%).

significant fraction of them underwent upfront surgery at the time of diagnosis.

The increasing occurrence of small, asymptomatic, NF-PanNETs and the demonstration of their relatively indolent behavior initiated a reconsideration of a routine surgical treatment of these entities. In 2012, Lee et al[8] reported that small NF-PanNETs exhibit minimal or no growth over a long-term period and that nonoperative management for these entities could be feasible and safe. Moreover, a nonoperative approach was advocated by the ENETS guidelines in the same year, suggesting an intensive 3-month follow-up for the first year and a 6-month observation up to 3 years after diagnosis. Since then, several other studies confirmed that a wait-and-see approach may be safely recommended, at least in a fraction of this group of patients.[6,9–13]

On the other hand, this watchful attitude was challenged by other authors who supported a more aggressive management because of the measurable risk of malignant features that could be present even among small NF-PanNETs.[17–19] A recent meta-analysis[17] highlighted that for every 5 patients followed up, 1 additional patient with N1 NF-PanNET would remain incorrectly followed.

Surprisingly, in the present experience one-third of the entire cohort of patients who had a diagnosis of incidentally discovered NF-PanNET ≤2 cm underwent surgery even though the management was based on the ENETS guidelines. This rate is consistent with that reported elsewhere.[9–11] Recently, Sadot et al[11] reported that, among 104 patients with small, asymptomatic PanNET who underwent observation, no patient developed evidence of metastases or died from disease. Nevertheless, it should be pointed out that all these studies considered earlier periods of recruitment as compared with the current series. More recently, a multicentrer study demonstrated that observation is yet not a well-accepted option among German surgeons.[28] Of note, in this study[28] only patients with PanNETs who underwent surgery between 2013 and 2017 were considered and the authors reported that one-third of these patients had a lesion ≤2 cm and were mostly asymptomatic. There are several reasons behind a surgical attitude toward these small, asymptomatic tumors despite evidence seeming to demonstrate their indolent behavior.

In the present series two important reasons for taking a surgical approach were the initial tumor size and the patients' age at the time of diagnosis. Patients who underwent surgery had larger tumors and were significantly younger compared with those who underwent surveillance. A possible explanation is that the natural history in the long-term period of these small lesions remains unknown. The majority of the published series reported a period of observation shorter than 5 years, and no reliable predictors of tumor progression have been demonstrated so far. Therefore, it is unclear whether the growth of small NF-PanNETs can be considered time dependent. Undoubtedly, the lack of robust data about the natural history of these tumors affected the confidence in conservative management also from a patients' perspective. Of note, one-third of patients who had a relative indication for surgery preferred to avoid a conservative treatment and they underwent pancreatic resection. This is consistent with Sadot et al[11] who observed that in the 30% of patients who underwent subsequent surgery during observation for small NF-PanNET, the main indication was patients' preference. Another factor that likely contributed to the high rate of surgical resection was the extensive use of diagnostic procedures such as EUS+FNA and ^{18}F-FDG-PET, which in different cases oriented the management toward a more aggressive attitude. In particular, all the patients who were referred to our group with a measurable hypervascularized nodule detected at morphologic imaging who had not undergone functional imaging were investigated with a combined ^{68}Ga and ^{18}F-FDG-PET or with an EUS+FNA. In nearly half of the cases, the final diagnosis was obtained by a cytologic evaluation, although it was possible to determine the value of Ki67 only in one-third of them. The cytologic diagnosis of a NF-PanNET G2 was determinant for a surgical approach in 4 patients. Notably, in only 1 case the final histologic report confirmed the cytologic tumor grading, whereas the remaining 3 tumors were eventually reclassified as G1. This result demonstrates that cytologically determined tumor grading should be taken extremely cautiously in these small neoplasms. On the other hand, other studies have demonstrated a good concordance between cytologic and histologic evaluation of Ki67.[29,30] Recently, Milione et al[31] reported that Ki67 is a powerful prognostic marker irrespective of the primary tumor size, demonstrating also that Ki67 can be assessed on presurgical biopsies with a high concordance rate with respect to surgical specimens. Moreover, the authors suggest that a presurgical evaluation of Ki67 should be included in the algorithm guiding clinical decision on resection of NF-PanNETs smaller than 2 cm. Nevertheless, in the study by Milione et al,[31] only 5 patients with pT1 NF-PanNET had a Ki67 >3%. Moreover, it should be also pointed out that in the present

series, a Ki67 measurement was feasible only in half of the performed FNA. This demonstrates that the possibility to obtain preoperatively a reliable assessment of tumor grading in such small lesions has to be questioned.

Functional imaging represents another important tool for assessing the grading of NF-PanNETs. In particular, ^{68}Ga-PET is usually positive in the presence of well-differentiated lesions, whereas ^{18}F-FDG-PET is more accurate for detecting the presence of high-grade NF-PanNET-NEC.[32] Although the diagnostic value of combined ^{68}Ga-PET and ^{18}F-FDG-PET has been established in patients affected by metastatic PanNET, it is unknown which is the value of a dual-tracer imaging in the presence of small and localized tumors. In the current study, the presence of a ^{18}F-FDG-PET positive NF-PanNET was an important determinant for a surgical approach. Nevertheless, only one-third of patients with an ^{18}F-FDG-PET positivity had at least one histologic feature of aggressiveness. On the contrary, the presence of MPD dilatation was often associated with malignant features at histologic examination. Although this represents a rare condition, it has to be promptly recognized because it is usually associated with a high risk of malignant behavior.[33,34] This so-called "sclerosing variant" has distinct pathologic features and biomarker expression profiles that are usually associated with more advanced stages.[35] Notably, the only two patients with nodal metastases at final pathologic exam also had an MPD dilated that represented the main indication for surgery. This finding also confirms that the risk of nodal involvement in an NF-PanNET smaller than 2 cm is extremely rare in the absence of preoperative worrisome features. From a surgical standpoint, a lymphadenectomy in the presence of small NF-PanNET is probably not necessary except when clear signs of local invasiveness are present.

A last interesting finding is related to the group of patients who were managed with an active surveillance. The present study corroborated other results[6,9–13] regarding the low rate of tumor growth and the safety of a conservative attitude in these patients. This was not the only element in favor of a wait-and-see strategy. The rate of pancreatic fistula after surgery was relatively high in the present series, thus confirming that the operative risk in these patients should be carefully weighed. Indeed, NF-PanNETs are frequently associated with a soft pancreatic texture and a small main pancreatic duct.

The strength of the present study is the relatively large cohort of patients collected in a single institution. This allowed a higher standardization of the initial diagnostic workup as well as a defined protocol of follow-up. Moreover, our group had elsewhere demonstrated the feasibility and the safety of observing asymptomatic NF-PanNET $\leq$2 cm,[12] and active surveillance was adopted as the treatment of choice in these cases. Of note, 5 patients who had a significant tumor growth during observation did not undergo subsequent surgery. This may be related to several reasons, such as comorbidities, slow growth rate over time, and patients' preferences. Moreover, because of the relatively short period of follow-up of the present and earlier reports,[6,9–13] firm conclusions regarding the extent and the duration of surveillance cannot be drawn. For this reason, an active surveillance is necessary to recognize in a timely fashion a significant increase of NF-PanNET and it cannot be interrupted in any patients until robust data on the natural history of these lesions are available. In this setting, the ongoing prospective observational study Asymptomatic Small Pancreatic Endocrine Neoplasm (ASPEN-www.clinicaltrials.gov/ct2/show/NCT03084770) will provide stronger evidences regarding the long-term outcome of this type of lesions.

The present study has several limitations. First, it is limited by its retrospective nature with inherited biases. In particular, the reason behind a surgical approach may have been influenced by several factors that could have not been well recognized retrospectively. Second, the relatively short follow-up period does not allow for any speculations regarding the natural history of small NF-PanNETs when observed. Finally, not all the patients received the same initial workup because some of them had been diagnosed in other institutions.

In conclusion, an active surveillance of small, asymptomatic, NF-PanNETs is safe; however, routine conservative management is still difficult to be systematically offered to all the patients. An extensive diagnostic workup, including functional imaging and cytologic assessment, is associated with a high risk of false-positive findings and therefore should be avoided. Therefore, patients with an asymptomatic NF-PanNET $\leq$2 cm who can be safely observed should not routinely undergo EUS+FNA or ^{18}F-FDG-PET. Because of the good outcomes of a watchful strategy, clinicians should adhere more firmly to the guidelines and not allow factors, such as age and patient's preference, to influence the decision whether to proceed with surgical resection.

Conflict of interest

The authors have indicated that they have no conflict of interest regarding the content of this article.

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