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**EDITORIAL**

- 149 Laparoscopic surgery for complex and recurrent Crohn's disease  
*Sevim Y, Akyol C, Aytac E, Baca B, Bulut O, Remzi FH*

**MINIREVIEWS**

- 153 Non-functioning pancreatic neuroendocrine tumors: Surgery or observation?  
*Bar-Moshe Y, Mazeh H, Grozinsky-Glasberg S*

**ORIGINAL ARTICLE**

**Case Control Study**

- 162 Comparative study of outcomes following laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy in morbidly obese patients: A case control study  
*Garg H, Priyadarshini P, Aggarwal S, Agarwal S, Chaudhary R*

**Retrospective Cohort Study**

- 171 Does serotonin reuptake inhibitor therapy increase the risk of post-sphincterotomy bleeding in patients undergoing endoscopic retrograde cholangio-pancreatography?  
*Yadav D, Vargo J, Lopez R, Chahal P*

**Retrospective Study**

- 177 Does deep sedation with propofol affect adenoma detection rates in average risk screening colonoscopy exams?  
*Thirumurthi S, Raju GS, Pande M, Ruiz J, Carlson R, Hagan KB, Lee JH, Ross WA*

- 183 Endoscopic balloon catheter dilatation *via* retrograde or static technique is safe and effective for cricopharyngeal dysfunction  
*Chandrasekhara V, Koh J, Lattimer L, Dunbar KB, Ravich WJ, Clarke JO*

- 189 Analysis of the risk factors for severity in post endoscopic retrograde cholangiopancreatography pancreatitis: The indication of prophylactic treatments  
*Matsubara H, Urano F, Kinoshita Y, Okamura S, Kawashima H, Goto H, Hirooka Y*

**Observational Study**

- 196 Endoscopic assessment and management of sporadic duodenal adenomas: The results of single centre multidisciplinary management  
*Rajkomar K, Kweon M, Khan I, Frankish P, Rodgers M, Koea JB*

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## Non-functioning pancreatic neuroendocrine tumors: Surgery or observation?

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neuroendocrine tumors are increasingly diagnosed on imaging studies performed for unrelated purposes. Although their resection is usually recommended, controversy still exists regarding their optimal management, due to their highly variable and difficult to predict biologic behavior. Recently, several studies and guidelines advocated an expectant management approach in small size, low grade, incidentally diagnosed nonfunctional pancreatic neuroendocrine tumors. The aim of this study is to review and summarize the available literature addressing nonfunctional pancreatic neuroendocrine tumors, with an emphasis on surgical management controversies.

**Key words:** Pancreatic neuroendocrine tumors; Nonfunctional; Incidental; Surgery; Observation

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**Core tip:** Nonfunctional pancreatic neuroendocrine tumors are increasingly diagnosed. Controversy exists regarding their optimal management. Expectant management in small size, low grade, incidentally diagnosed non-functional pancreatic neuroendocrine tumors has been suggested as an optional treatment. The aim of this study is to review the available literature addressing nonfunctional pancreatic neuroendocrine tumors, with an emphasis on surgical management controversies.

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### Abstract

Incidentally detected, sporadic, nonfunctional pancreatic

### INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are un-

common neoplasms that arise from the islet cells of the pancreas and represent 1%-2% of all pancreatic cancers<sup>[1]</sup>. PNETs are clinically classified as functional (F-PNETs) and non-functional (NF-PNETs) based on the existence or non-existence of symptoms caused by hormone hypersecretion<sup>[2]</sup>. F-PNETs can synthesize and produce hormones such as insulin, gastrin, glucagon, somatostatin, and vasoactive intestinal peptide (VIP) resulting in myriad clinical syndromes. NF-PNETs, on the other hand, may secrete some peptides such as chromogranin, pancreatic polypeptide, and others, but without clinical syndromes of hypersecretion<sup>[3,4]</sup>. Historically, F-PNETs were reported to have increased incidence and earlier diagnosis as compared to NF-PNETs due to their symptoms of hypersecretion, although the later accounts for the majority of PNETs<sup>[5-7]</sup>. With the widespread use and improvement of cross-sectional imaging techniques, NF-PNETs are increasingly discovered incidentally in asymptomatic patients who undergo evaluation for unrelated conditions<sup>[8,9]</sup>. This has been accompanied by an increase preoperative histologic diagnosis through endoscopic ultrasonography (EUS) and EUS-guided fine needle aspiration<sup>[10]</sup>. While there is a unanimity consensus that favors surgical resection in F-PNETs, controversy exists among clinicians regarding the optimal management of asymptomatic, small, incidentally discovered NF-PNETs. This article provides an updated review and aims to address the controversies in the management of sporadic small NF-PNETs. In light of article scope limitations, management and treatment of advanced metastatic disease or familial related diseases will not be addressed in this review.

## EPIDEMIOLOGY

PNETs are more common in Caucasian and in males, with an incidence that increases with age, reaching a pick in the fifth-sixth decades. Detection is increasing owing to the widespread use of axial imaging, with one retrospective study demonstrating more than 2-fold increase in the incidence of NF-PNETs compared to 16 years ago and that the increase is related to accidental detection of the tumors<sup>[8,11]</sup>. NF-PNETs are biologically diverse and account for 65% to 90% of PNETs<sup>[1,12,13]</sup>.

While most of PNETs occur sporadically, 10%-30% of them are associated with various inherited disorders including MEN1, Von Hippel-Lindau syndrome, neurofibromatosis 1, tuberous sclerosis, and Mahvash disease<sup>[14,15]</sup>. The majority of PNETs related to MEN1 and VHL syndromes are non-functioning tumors<sup>[1]</sup>.

## CLINICAL PRESENTATION

Patients with F-PNETs have overt clinical symptoms due to their physiologic response to hormone hypersecretion. In contrast, NF-PNETs can remain asymptomatic before they reach a significant tumor burden. Thus, they often present later during the disease with symptoms

of local compression or metastatic disease in 21% and 60%, respectively<sup>[1,6,16]</sup>. When symptomatic, the main complaints observed are abdominal pain (35%-78%), weight loss (20%-35%), and anorexia and nausea (45%). Less frequent signs include icterus (17%-50%), intraabdominal hemorrhage (4%-20%), or a palpable mass (7%-40%)<sup>[17]</sup>. Up to 50% of non-metastatic NF-PNETs will not show any symptoms being diagnosed incidentally on cross-sectional imaging performed for other indications<sup>[8,18]</sup>.

## DIAGNOSIS

The diagnostic approach of patients with NF-PNETs should be thorough and starts with detailed past medical and family history followed by complete physical examination. Then biochemical and imaging studies have uttermost importance for treatment strategy and are performed in order to evaluate the degree of local invasion, lymph node involvement, as well as the presence of metastatic disease.

## IMAGING

High-resolution computerized tomography (CT) scan is the initial imaging modality at many institutions due to its noninvasiveness and availability. Studies have reported a sensitivity of more than 80%, with a direct correlation to tumor size<sup>[19,20]</sup>.

Compared to CT, magnetic resonance imaging (MRI) has non-ionized radiation advantage and can be used as an alternative imaging modality. Furthermore, studies reported superiority of MRI over CT in detecting smaller pancreatic lesions and liver metastases<sup>[21,22]</sup>. One study reported a sensitivity and specificity of up to 85% and 100%, respectively<sup>[23]</sup>.

EUS is an additional imaging modality, and has additional benefits in preoperative diagnosis<sup>[24]</sup>. Somatostatin receptor imaging (SRI) is a functional imaging modality of choice in the evaluation of neuroendocrine tumors. Besides its utility in the staging of these tumors, SRI may help to select the patients with advanced disease that are suitable for systemic somatostatin-based therapies<sup>[25,26]</sup>.

While <sup>111</sup>Indium-DTPA-octreotide (Octreoscan) has been initially used, with the recent availability of the PET imaging technique, somatostatin analogues have been labeled with positron emitting isotopes, including Gallium-68, to image somatostatin receptor (SSR) expressing tumors<sup>[27]</sup>. The compounds often used in molecular imaging of NETs with PET are <sup>68</sup>Ga-DOTATOC, <sup>68</sup>Ga-DOTATATE, and <sup>68</sup>Ga-DOTANOC, with a varying affinity to different somatostatin receptors. It has been demonstrated that <sup>68</sup>Ga-DOTA-TATE PET CT scan has the highest affinity for SSR2 and can dramatically improve the spatial resolution in parallel with a significantly higher detection rate and accuracy compared to conventional Octreoscan<sup>[28,29]</sup>.

## BIOPSY

EUS-guided fine-needle aspiration biopsy can provide preoperative histologic information important for tumor grading. One meta-analysis reported a sensitivity of 87% and a specificity of 98%<sup>[30]</sup>. The utility of routine preoperative biopsy remains controversial. Some clinicians have argued that the theoretical risk of procedure complications outweighs the benefit, while others, including us, believe in routine biopsy given the importance of characterizing and grading the tumor. Dietrich *et al.*<sup>[31]</sup> demonstrated in a large study the importance of preoperative diagnosis. Among 394 patients with incidental finding of lesions smaller than ≤ 15 mm, all were diagnosed by imaging-guided biopsy and/or surgery, 156 (about 40%) were diagnosed with neuroendocrine tumors, 146 pancreatic ductal adenocarcinoma, and 92 with various other etiologies. Although retrospective, approximately 60% did not have pancreatic ductal adenocarcinoma and not necessarily require radical surgery that carries significant risks<sup>[31]</sup>.

## BIOCHEMICAL STUDIES

Chromogranin A (CgA) can be used as a nonspecific biochemical marker. It has an approximate sensitivity and specificity of 60% and 80%, respectively<sup>[32,33]</sup>. False positive elevations of CgA can present in many other conditions such as use of anti-acid drugs (*e.g.*, proton pump inhibitors, H2 blockers, *etc.*), atrophic gastritis, renal insufficiency, hepatic insufficiency, *ect.*<sup>[34]</sup>.

Pancreatic polypeptide (PP) and neuron specific enolase (NSE) are additional useful NF-PNET markers. As with CgA false positive elevations of pancreatic polypeptide can be postprandial and in renal insufficiency<sup>[16,32,35]</sup>. Preoperative increased levels of CgA or PP may potentially be helpful in evaluation of response, progression, or recurrence at an early stage<sup>[36]</sup>.

Elevated NSE levels were exclusively associated with poor tumor differentiation<sup>[36]</sup>.

## GRADING AND STAGING

From histological point of view, the 2010 World Health Organization (WHO) classification system is the most used grading system. It identifies three categories: Grade 1 tumors (< 2 mitosis/10 HPF and Ki-67 index ≤ 2%), grade 2 (2-20 mitosis/10 HPF and Ki-67 index 3%-20%), and grade 3 (> 20 mitosis/10 HPF and Ki-67 index of > 20%). This classification forms the basis for evaluating prognosis and predicting malignancy<sup>[2,37]</sup>.

Two TNM based staging systems were developed for PNETs, one from the American Joint Committee on Cancer (AJCC) that covers both pancreatic exocrine and neuroendocrine malignancies and the other proposed by the European Neuroendocrine Tumor Society (ENETS) (Table 1)<sup>[38,39]</sup>. The difference between them is mainly expressed in the soft tissue involvement criteria. While the AJCC characterize T3-T4 using peripancreatic

invasion of these tumors (sometimes difficult to assess due to the structure of the pancreas), the ENETS staging system relies on more assessable criteria such as tumor size<sup>[40,41]</sup>. Despite differences, both staging systems are highly prognostic validated and found to be useful for clinical practice<sup>[42-44]</sup>.

One retrospective 11-year period report of 425 patients with PNETs demonstrated that the 5-year overall survival rates using the ENETS classification for patients treated in referral neuroendocrine tumor (NET) center for stages I, II, III and IV disease were 100%, 88%, 85%, and 57%, respectively. The corresponding values using the AJCC classification were 92%, 84%, 81%, and 57%, respectively<sup>[44]</sup>. Another large cohort study of 1072 post-operative patients suggests the ENETS TNM staging system is superior to the AJCC and WHO 2010 TNM staging system and supports its use in clinical practice<sup>[42]</sup>.

## CURRENT GUIDELINES

Several guidelines for the management of PNETs have been established in order to help physicians treating these complex patients. The 2012 and 2016 European Neuroendocrine Tumor Society (ENETS) guidelines, the National Comprehensive Cancer Network 2016 (NCCN), North American Neuroendocrine Tumor Society-2013 (NANETS), and European Society of Medical Oncology-2012 (ESMO) have published diagnostic and therapeutic guidelines<sup>[3,12,45-47]</sup>.

For initial biochemical workup the ENETS, ESMO, and NANETS guidelines all recommend measuring CgA and PP serum levels as a useful tool for reaching a diagnosis in a fraction of NF-PNETs.

The first imaging modality recommended is multi-phasic CT/MRI with contrast agents imaging modality, while octreotide scintigraphy (planar and SPECT) but mainly <sup>68</sup>Ga-labeled somatostatin analogues with PET/CT are also recommended, if available.

All four guidelines recommend using the 2010 WHO grading system as the grading of choice and generally advocate surgical resection as the preferred option as long as there are no surgical limiting contraindications, highly diffuse metastatic disease, or selected cases that can be observed discussed in the next sections.

The surgical options for locoregional NF-PNETs mentioned in all guidelines range between simple enucleation, central pancreatectomy, distal pancreatectomy with or without splenectomy, and pancreatoduodenectomy (Whipple's operation). The extent and type of surgery mainly depends on the location of the primary tumor (head, body, or tail). Tumors larger than 2 cm that are locally invasive or have positive lymph node involvement in preoperative evaluation should all include regional lymph node dissection. In patients with smaller than 2 cm NF-PNETs, lymph node sampling is not always mandatory. While both NCCN and ENETS recognize the role of laparoscopic approach in PNETs resections, the EMCO guidelines do not recommend this approach due to the need for thorough intraoperative lymph node

**Table 1** European Neuroendocrine Tumor Society and American Joint Committee on Cancer TNM grading systems for pancreatic tumors<sup>[38,39]</sup>

	ENETS	AJCC
<b>T Grade (primary tumor)</b>		
Tx	Primary tumor is not assessed	Primary tumor is not assessed
T0	No finding of primary tumor	No finding of a primary tumor
Tis		<i>In situ</i> carcinoma
T1	Tumor is limited to the pancreas and < 2 cm	Tumor is limited to the pancreas and ≤ 2 cm
T2	Tumor is limited to the pancreas and 2 to 4 cm	T2 tumor is limited to the pancreas and > 2 cm
T3	Tumor is limited to the pancreas and > 4 cm or with positive duodenum or biliary tract invasion	Tumor has progressed beyond the pancreas but there is no celiac or mesenteric artery involvement
T4	Tumor has invaded the neighboring organs (stomach, spleen, colon, adrenal gland) or walls of the large vessels (celiac artery or superior mesenteric artery)	Tumor shows celiac or superior mesenteric artery involvement
<b>N-lymph node status</b>		
Nx	Regional lymph nodes are not assessed	Regional lymph nodes are not assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis is positive	Regional lymph node metastasis is positive
<b>M-distant metastasis</b>		
Mx	Distant metastasis is not assessed	
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis is positive	Distant metastasis is positive
<b>Stage</b>		
0		Tis, N0, M0
I	T1, N0, M0	
IA		T1, N0, M0
IB		T2, N0, M0
IIA	T2, N0, M0	T3, N0, M0; T1, N1, M0
IIB	T3, N0, M0	T2, N1, M0; T3, N1, M0
III		T4, Any N, M0
IIIA	T4, N0, M0	
IIIB	Any T, N1, M0	
IV	Any T, Any N, M1	Any T, Any N, M1

inspection.

Currently, updated ENETS and NCCN guidelines both acknowledge nonoperational options, with different tumor size-cutoff (NCCN < 1 cm, ENETS < 2 cm), as suitable for managing small NF-PNETs while taking into account factors such as incidental discovery, lack of clinical syndromes and radiological signs suspicious for malignancy, as well as patient's characteristics (surgical risk, comorbidities, and personal wishes)<sup>[12,45,47]</sup>. However, data supporting this non-operational option are controversial and will be reviewed in the next section. Figure 1 offers a suggested algorithm for patient management.

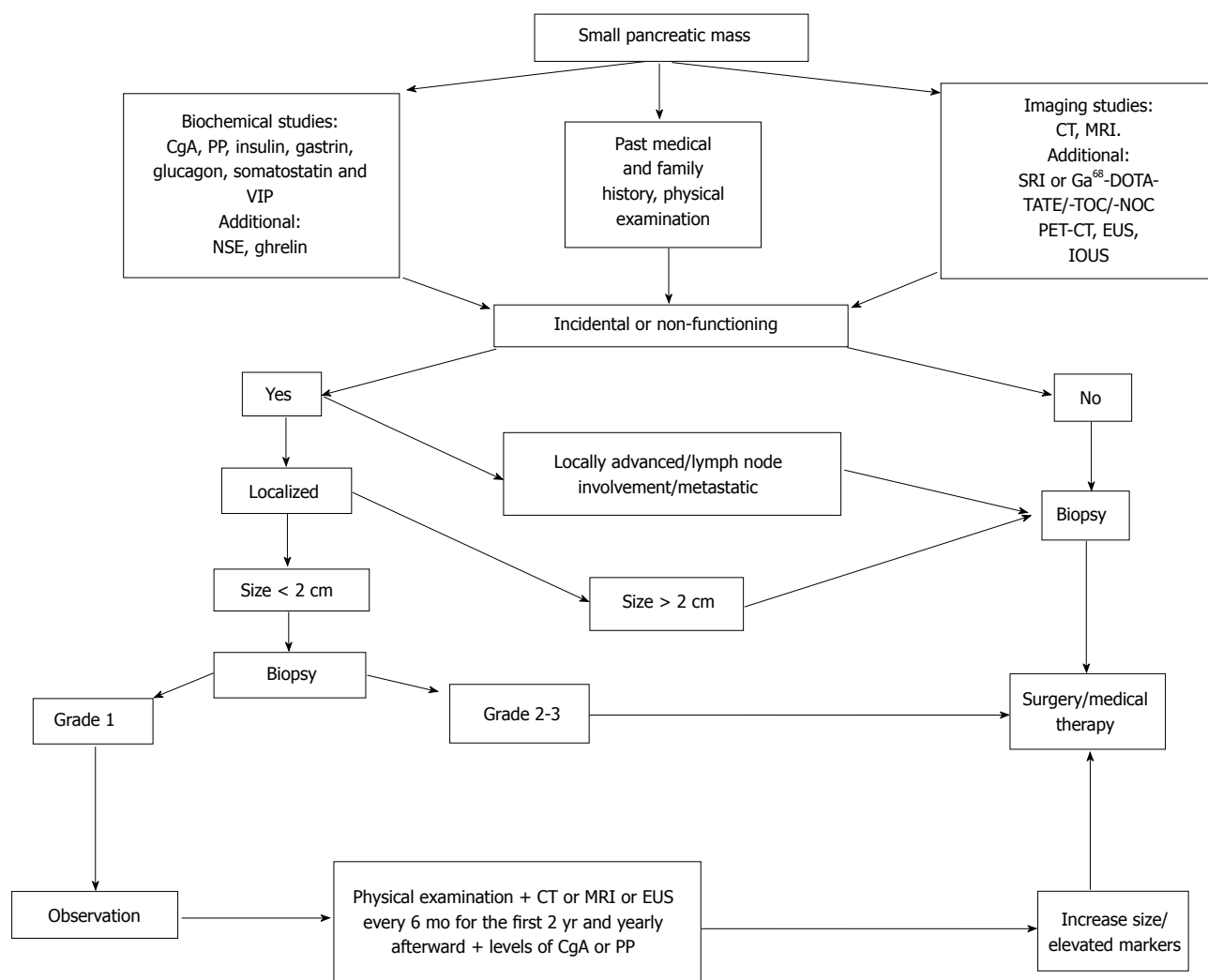
## SURGICAL MANAGEMENT CONTROVERSY

In most cases surgery remains the curative modality of choice for NF-PNETs, with preliminary evidence demonstrating improved survival especially with localized disease<sup>[48,49]</sup>. However, as previously mentioned, during the last recent years there is a significant increase in the detection of small, incidentally discovered, asymptomatic NF-PNETs, that may be managed conservatively by observation. At present there are no RCTs or meta-analyses that can assist to outline the optimal approach for

the management of such small NF-PNETs. Nevertheless, there are 12 retrospective series that may shed some light on this controversy.

### **Tumor size as criteria for treatment decision**

Bettini *et al.*<sup>[50]</sup> demonstrated a distinct correlation between tumor size and lower malignancy potential on 177 patients, who were divided into three groups depending on tumor size (≤ 2 cm, 2-4 cm, > 4 cm), all underwent curative resection. Patients with tumor ≤ 2 cm ( $n = 51$ ) had higher frequency of incidental diagnosis compared with patients with > 4 cm (57% vs 32%,  $P = 0.014$ ). Among those who were incidentally discovered, only 6% were malignant and none died from the disease. In addition, a correlation between tumor size and Ki67 was demonstrated. Patients with tumors ≤ 2 cm had lower Ki67 median values compared with patients with tumors > 2 cm ≤ 4 cm and > 4 cm (1% vs 2% and 3%, respectively). The authors suggested that nonsurgical management could be advocated in selected cases for low-grade tumors less than 2 cm, due to their indolent course. In an attempt to determine the prognostic value of indicators of malignancy in NF-PNETs ≤ 2 cm, Regenet *et al.*<sup>[51]</sup> demonstrated, by using multivariate analysis, that tumor size is a significant indicator of malignancy, and



**Figure 1 Suggested algorithm for the management of small pancreatic mass.** CgA: Chromogranin A; PP: Pancreatic polypeptide; VIP: Vasoactive intestinal peptide; NSE: Neuron-specific enolase; CT: Computed tomography; MRI: Magnetic resonance imaging; SRI: Somatostatin-receptor imaging; EUS: Endoscopic ultrasonography; IOUS: Intraoperatively ultrasonography; PET: Positron emission tomography; Ga<sup>68</sup>-DOTA-TATE/-TOC/-NOC: <sup>68</sup>Gallium-DOTA-TATE, <sup>68</sup>Gallium-DOTA-TOC<sup>68</sup> and Gallium-DOTA-NOC respectively.

even proposed a new 1.7 cm cutoff as more accurate for prediction of malignancy potential with a sensitivity of 92% and specificity of 75%. Despite these findings, Ki67 was not found to be a significant indicator of malignancy probably due to large number of patients without complete histologic assessment and Ki67 evaluation<sup>[51]</sup>. In a larger population study by Gratian *et al*<sup>[52]</sup> among 1854 patients with NF-PNETs  $\leq 2$  cm, who were identified from the National Cancer Data Base (NCDB), 309 patients (29%) presented with regional lymph node involvement and 180 patients (10%) presented with distant metastases<sup>[52]</sup>. In contrast to Bettini *et al* findings, they conclude that tumors smaller than 2 cm have a significant risk of malignancy. It is worth mentioning that the study was limited by missing data of several variables, including Ki67.

#### **Incidental vs non-incident diagnosis as criteria for treatment decision**

Different studies have recently tried to distinguish

between incidental and non-incident NF-PNETs, especially those discovered at early age, in terms of prognosis and treatment approach. Cheema *et al*<sup>[18]</sup> identified 143 nonmetastatic PNETs, 40% were diagnosed incidentally. They demonstrated that 5-year progression free survival (PFS) was significantly prolonged in patients with incidental diagnosed vs symptomatic tumors (86% vs 59%,  $P = 0.007$ ).

#### **Tumor grading as criteria for treatment decision**

It should be noted that histopathologic grade was another statistically significant factor for progression on multivariate analysis (hazard ratio of 3.0 for Grade 2 vs Grade 1,  $P = 0.007$ ), though Ki67 proliferation index was only evaluated in 25% of cases<sup>[18]</sup>. As opposed to Cheema *et al*<sup>[18]</sup>, Haynes *et al*<sup>[53]</sup> described 139 patients who all underwent surgery and identified no large difference in tumor size (3.0 cm vs 3.5 cm,  $P = 0.48$ ), frequency of malignant histopathologic findings (28% vs 30%), or 5-year PFS (83% vs 82%,  $P = 0.27$ ).



**Table 2** Retrospective studies regarding incidental discovery

Ref.	Study period	Patients (n)	Group	Number of patients n (%)	5-yr PFS rates (%)	P value	Median follow-up time (mo)
Cheema <i>et al</i> <sup>[18]</sup>	1999-2010	143	Incidental	56 (40)	86	0.07	67 (mean)
			Non-incidental	87 (60)	59		
Crippa <i>et al</i> <sup>[54]</sup>	1990-2009	355	Incidental	124 (35)	83	< 0.001	44
			Non-incidental	231 (65)	32		
Haynes <i>et al</i> <sup>[53]</sup>	1997-2009	139	Incidental	109 (82)	82.8	0.27	34.2
			Non-incidental	30 (18)	81.7		
Birnbbaum <i>et al</i> <sup>[55]</sup>	1994-2010	108	Incidental	65 (61)	92	0.03	42
			Non-incidental	43 (39)	82		

between incidental and non-incidental groups<sup>[18,53]</sup>. Of the 39 patients with tumors  $\leq 2$  cm, 3 patients (7.7%) had late metastases or recurrence. Though problematic due to lack of observational group, they concluded that all patients should undergo tumor resection, even in incidentally discovered NF-PNETs smaller than 2 cm. From a staging point of view Crippa *et al*<sup>[54]</sup> demonstrated in a larger ( $n = 355$ ) retrospective study that NF-PNETs diagnosed incidentally have greater 5-year PFS rates in all stages than symptomatic tumors: Stage I (97% vs 78%,  $P = 0.013$ ), stage II (93% vs 74%,  $P = 0.036$ ), stage III (69% vs 27%,  $P < 0.0001$ ), and stage IV (60% vs 17%,  $P = 0.112$ ). On multivariate analysis Grade 2 NF-PNETs was found to be a predictor of PFS among 124 incidentally diagnosed patients, with a hazard ratio of 3.402 (95%CI: 0.92-12.57,  $P = 0.066$ ). In addition, they reported that 12 excluded patients, who underwent non-operative management of incidental NF-PNETs and had no tumor progression after median follow up of 36 mo. In this small group of patients the median tumor size at diagnosis was 1.4 cm (range 1.0-2.9 cm), and was stable throughout the surveillance period. Similar PFS rates were demonstrated in another retrospective study by Birnbbaum *et al*<sup>[55]</sup> that included 106 patients, 65 discovered incidentally. These patients demonstrated both higher incidence of tumors smaller than 2 cm (65% vs 42%,  $P = 0.019$ ) and lower Ki67 proliferation index (1% vs 4%,  $P = 0.004$ ) compared to symptomatic patients. The authors concluded that pancreas sparing surgery is recommended as an optional treatment for these incidental NF-PNETs, due to less aggressive characteristics compared with symptomatic tumors (Table 2).

### Observation for selected patients

Several retrospectively designed studies tried to answer the question whether observational management is suitable for NF-PNETs smaller than 2 cm and to assess the risk-benefit balance of this approach. Gaujoux *et al*<sup>[56]</sup> published a series of 46 patients who were followed for at least 18 mo (median 34, range 24-52 mo) with an average of four (range 4-6) serial imaging sessions or followed up after resection<sup>[56]</sup>. Among the resection group ( $n = 8$ ), all grade 1 and without lymph node involvement, 5 were resected upon initial diagnosis and only 3 were resected due to tumor enlargement

under imaging observations. The remaining 38 patients, who were managed without surgery, did not show any significant characteristics of malignancy such as distant metastases, nodal involvement, or significant increase in tumor size. In this study the overall median tumor growth was 0.12 mm per year. Both Lee *et al*<sup>[57]</sup> and Rosenberg *et al*<sup>[58]</sup> published similar results where small NF-PNETs in either the operative or non-operative groups demonstrated no evidence of progression, with lower, though important, operational-morbidity related rates (46% and 35%, respectively)<sup>[57,58]</sup>. They both conclude that non-operative management may be advocated and safe in selected patients. In the Lee *et al*<sup>[57]</sup> study, both surgical and nonsurgical group's tumors had low or intermediate grade and Ki67 values smaller than 5%, in all patients with available results<sup>[57]</sup>. Rosenberg *et al*<sup>[58]</sup> published a 35 patients series divided into operative and non-operative groups as well: Ki67 proliferation index rates of < 2% and 3%-20% were 65% vs 0% and 30% vs 27%, respectively. Ki67 data was not available in 1 (5%) patient in the operative group vs 11 (73%) in the non-operative group<sup>[58]</sup>.

The observational approach for certain tumors was reinforced by another recently published matched case-control study by Sadot *et al*<sup>[59]</sup> who demonstrated that 5-year PFS was 95% and 91% ( $P = 0.3$ ) for observational and resection only groups, respectively. A quarter ( $n = 26$ ) of the observation group crossed over to resection group, due to different reasons. After a median follow-up of 7 years, none of these patients developed malignant features (node involvement or metastases). These data imply that initially observational approach and delayed surgical intervention may not compromise long-term outcomes.

Contrary to this claim, Sharpe *et al*<sup>[60]</sup> performed a population based study and demonstrated that patients who were managed with observation had nearly three times the risk of mortality in comparison to those who underwent resection<sup>[60]</sup>. Their study was large and based on patients collected from NCDB, all with NF-PNETs smaller than 2 cm. The authors concluded that surgical resection provides a benefit regardless of tumor grade, though it wasn't statistically proven at poorly differentiated/undifferentiated tumor. A summary of the studies regarding surgical vs observational approach in NF-PNETs is presented in Table 3.

**Table 3** Retrospective studies regarding surgery vs observational management

Ref.	Study period	Patients n	Group	Number of patients n (%)	Median follow-up time (mo)	Surgery morbidity rate (%)
Gaujoux <i>et al</i> <sup>[56]</sup>	2000-2011	46	Observational	38 (83)	> 18	62
			Surgery	8 (17)	27	
Lee <i>et al</i> <sup>[57]</sup>	2000-2011	133	Observational	77 (57)	44 (Mean)	46
			Surgery	56 (43)	52 (Mean)	
Rosenberg <i>et al</i> <sup>[58]</sup>	1999-2014	35	Observational	15 (42)	28	35
			Surgery	20 (58)	34	
Sharpe <i>et al</i> <sup>[60]</sup>	1998-2006	380	Observational	71 (19)	60	N/A
			Surgery	309 (81)	60	
Sadot <i>et al</i> <sup>[59]</sup>	1993-2013	181	Observational	104 <sup>2</sup> (57)	44	N/A
			Surgery	77 <sup>1</sup> (43)	57	

<sup>1</sup>Matched group; <sup>2</sup>Before cross over; N/A: Not available.

## OBSERVATION PROTOCOL

History and physical examination, as well as biochemical markers and conventional trans-sectional high-resolution imaging should be used for both non-operative and postoperative surveillance. Postoperatively in patients with NF-PNETs grade 1 and 2, imaging is indicated every 3-9 mo (CT, MRI, or EUS), while more frequent imaging (up to 2-3 mo intervals periods) is indicated in Grade 3 or recurrent symptomatic patients, during the first year following surgery<sup>[12,45,47,61]</sup>. Either Octreoscan or PET/CT using <sup>68</sup>Ga-DOTA-TOC/-NOC/-TATE should be repeated every 18-24 mo for grades 1-2<sup>[61]</sup>. In non-surgical patients with less than 2 cm NF-PNETs, Gaujoux *et al*<sup>[56]</sup> recommend conventional contrast enhanced CT or MRI every 6 mo for the first 2 years and yearly afterward<sup>[56]</sup>. In patients who underwent surgical resection of the tumor, imaging at 6-12 mo intervals should be performed between one and ten years post resection, although the optimal duration surveillance time for either non-operative nor postoperative patients is unknown<sup>[46]</sup>.

## CONCLUSION

In the last two decades the incidence of small NF-PNETs neoplasms has been steadily increasing. Unfortunately, there are still no clear prognostic factors that can enable us to distinguish between tumors suitable for observation and tumors with greater malignant potential that should be treated more aggressively. Several retrospective population based studies were reviewed in this article in an attempt to reduce the uncertainty. However, issues of selection bias, small sampling, and lack of data that are inherent in this type of studies limit our ability to conclude valid recommendations. In our NET center, the decision on treatment approach (follow-up vs surgical excision) for incidental NF-PNETs patients is based on tumor size (less or more than 2 cm), tumor grading, intensity of uptake on functional imaging (<sup>68</sup>GaDOTATATE-PET/CT), on the stage of the disease, as well as on patient's desire. Larger scale, preferably multicenter randomized control trials, are needed in order to clarify the optimal management strategy and

treatment for these rare small incidentally discovered tumors.

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