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REVIEW ARTICLE

Surveillance strategy for small asymptomatic non-functional pancreatic neuroendocrine tumors – a systematic review and meta-analysis

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Abstract

Background: Non-functional pancreatic neuroendocrine tumors (NF-PNET) are rare neoplasms being increasingly diagnosed. Surgical treatment or expectant management are both suggested for small NF-PNETs. The aim of this study was to evaluate the outcome of surveillance strategy for small NF-PNETs.

Methods: A systematic search was performed up to March 2016 in MEDLINE, EMBASE and the Cochrane Library according to the PRISMA guidelines. Data was pooled using the random-effects model.

Results: Nine articles including 344 patients with sporadic and 64 patients with MEN1 related NF-PNET were selected. Tumor growth was observed in 22% and 52%, development of metastases were reported on 0% and 9%, and rate of secondary surgical resection was 12% and 25% in patients with sporadic or MEN1 related NF-PNETs, respectively. All metastases (1 distant, 4 nodal) were reported by a single study in patients with MEN1. Reason for secondary surgery was tumor growth in half of patients undergoing surgery.

Discussion: Expectant management of small asymptomatic, sporadic, NF-PNETs could be a reasonable option in highly selected patients. However, the level of evidence is low and longer follow-up is needed to identify patients could benefit from upfront surgery instead of expectant treatment.

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Introduction

Pancreatic neuroendocrine tumors (PNET) are rare neoplasms with highly variable prognosis that is mainly influenced by tumor size, secretion, histological grade, and stage at the time of diagnosis.[1] Large, high-grade tumors tend to have a poor prognosis, whereas smaller and lower grade tumors can be curatively treated.[2–5] Advances in modern imaging technology have contributed to widespread use of computed tomography (CT) and magnetic resonance imaging (MRI). This has resulted in increased incidence of multiple diseases and possibly led to overtreatment of patients.[6] PNET is one such finding that has become more common in the era of modern imaging technology.[7,8]

The paper is not based on a previous communication to a society or meeting.

There is a consensus that patients with symptomatic or large (>2 cm) PNETs should undergo pancreatic resection.[9,10] However, controversy exists whether to resect small (≤2 cm), asymptomatic, and non-functional PNETs (NF-PNET). Some authors advocate surgery for all PNETs,[11–13] while recently others suggest that small, asymptomatic NF-PNETs are safe candidates for surveillance.[14–17] Similarly, some guidelines recommend upfront surgery,[18] while others acknowledge surveillance as an option.[19–21]

The aim of this study was to systematically review the current literature reporting results of surveillance of small NF-PNETs.

Methods

Search strategy

A systematic review of literature published in PubMed, EMBASE, and Cochrane Database from January 2000 to 3rd March 2016 was performed. The following search strategy for the MESH and non-MESH heading was used: ("neuroendocrine tumor*" or carcinoid or ((neuroendocrine or "neuro-endocrine") AND (cancer* or carcinom* or malignan* or neoplas* or tumor* or tumour*))) AND (pancrea* AND (cancer* or carcinom* or malignan* or neoplas* or tumor* or tumour*) OR ("pancreas tumor*" or pnet*)). Filters were used to exclude animal studies and non-English articles. Only relevant studies were selected via search terms for specific studies (epidemiology studies, cohort studies, clinical trials, retrospective/prospective studies, case–control studies).

Eligibility criteria and data collection

Titles and abstracts of found articles were independently screened by three reviewers. Unpublished data, abstracts, and duplicate publications were excluded. Original clinical studies of any level of evidence in English language were considered. Article full-texts of putatively relevant articles were retrieved and further screened for articles dealing with surveillance of PNETs. These articles were read and analyzed for eligibility by two reviewers (SV, LLTYS) independently. Disagreement was settled with discussion and/or participation of a third reviewer in the discussion (GS). Only studies were included in the final analyses, which defined non-operative expectant management for small NF-PNETs that had no metastases at the time of diagnosis. Studies were excluded if i) the study reported less than 10 patients with expectant management, ii) median follow-up was less than 18 months or not reported, iii) expectant management included specific treatment (such as somatostatin analogs), iv) observation group included patients with metastatic disease, and if non-metastatic tumors were not reported separately, v) the study did not report non-functional and functional PNETs separately, vi) the study did not report patient characteristics of patients undergoing expectant management separately from patients undergoing upfront surgery, or vii) the study did not report the sizes of the tumors accurately or did not report small and large tumor separately.

Data extraction

Patients with sporadic and MEN1 related NF-PNETs are reported separately. Outcomes measured were proportion of patients with growth of tumor in follow-up, the need for pancreatic resection, and the development of metastases (lymph node or distant). Standardized forms were used by two independent researchers (SV, LLTYS) to extract the data. Data regarding basic patient characteristics, tumor characteristics, type of diagnostic work-up, follow-up, tumor growth, surgery during surveillance, development of metastases during surveillance, reason for expectant management, and follow-up protocol were extracted. Quality of the studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS)[22] by two independent reviewers (SV, LLTYS). Each study was assessed for eight MINORS items specifically designed for non-comparative studies with 0–2 points given each (total score 0–16). This article is reported in accordance with the guidelines set out by the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement.[23]

Statistics

Fixed and Random effect models of pooled proportions were performed using DerSimonian and Laird approach (Freeman-Tukey double arcsine transformation) by using R (R Foundation for Statistical Computing, Vienna, Austria). Ninety-five percent confidence intervals are presented for each effect measure. Heterogeneity was assessed by using the I^2 statistic. Funnel plots for proportion were used as an analytic tool to identify potential presence of publication bias using a Web-based software tool developed by APHO (Association of Public Health Observatories, www.apho.org.uk).

Results

Literature search

Literature search yielded 5440 articles, of which 107 full-texts were analyzed and finally 9 studies were included in the analyzes (Fig. 1). Eleven studies dealing with expectant management were excluded (Supplementary Table 1).

Characteristic of the studies

The nine included studies reported a total of 408 patients including 344 with a sporadic PNET and 64 with MEN-1 related PNET (Tables 1,2, Supplementatry Table 2). Median age ranged from 32 to 68 years undergoing expectant management of small NF-PNETs. Patients with MEN1-related tumors were younger (median age ranging 32–42) than patients with sporadic tumors (median age ranging 56–68) (Supplementary Table 2).

Six were single center studies, two included patients from two centers,[15,24] and one from four tertiary centers.[25] Study inclusion period varied between 11 and 32 years. Rationale for expectant management was disclosed in three studies (n = 76) and included the following reasons: small incidental tumor, patients' personal

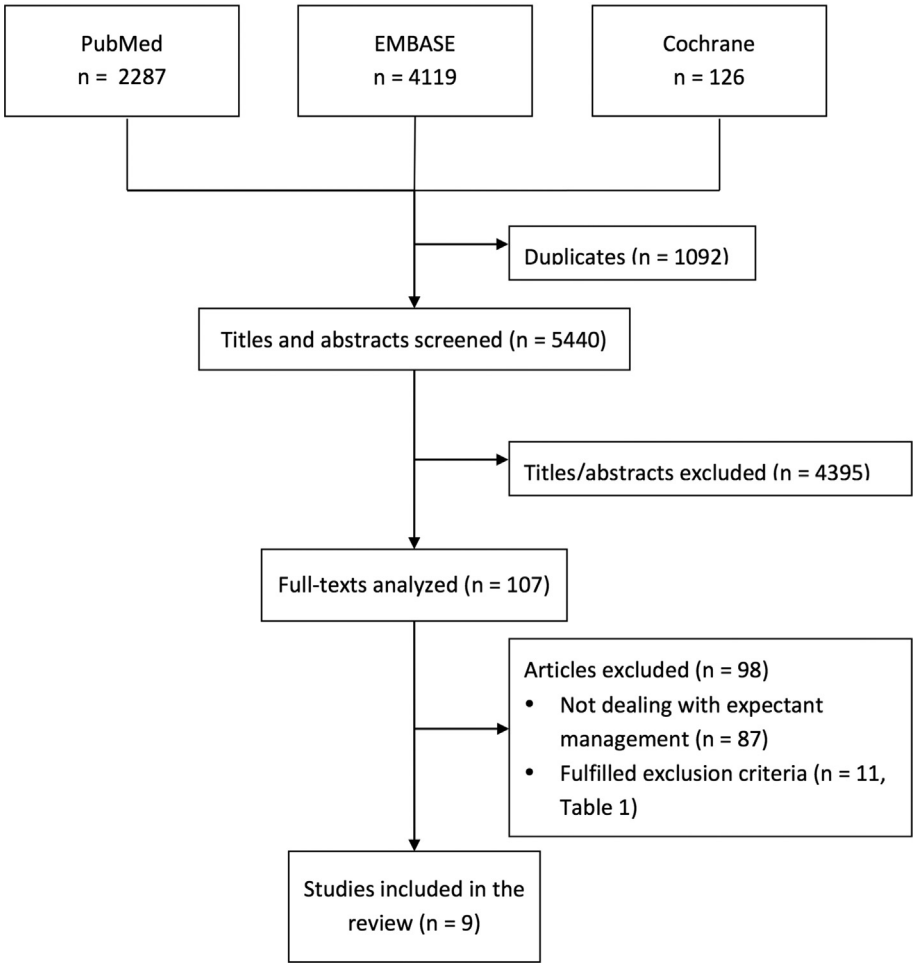

Figure 1 Flow chart illustrating the process of inclusion and exclusion of studies eligible for analysis in the review

choice, physician's preference, advanced age or comorbid condition, and patients opting for surgery, but had prior imaging fulfilling surveillance criteria in the study.[15,16,24] (Supplementary Table 2).

Quality assessment of studies

The quality of the studies varied from 7 to 10 points (44–63% of the maximum 16 points) according to MINORS criteria (Supplementary Table 2). Only one study included a prospective cohort,[26] while the rest were retrospective series. Five studies had insufficient endpoints; two studies did not report the proportion of tumor that showed growth,[17,26] two studies did not report how many patients developed metastases in follow-up,[27,28] and one study did not report the number of patients who needed surgery in follow-up.[24] Follow-up period was short in one study (median 20 months).[26] Funnel plots, evaluating the proportions of (sporadic) patients who experienced tumor growth or underwent resection, showed possible publication bias (Supplementary Fig. 1).

Characteristic of the patients

Six studies reported almost only sporadic NF-PNETs (1 of 344 patients had VHL (0.3%)), and are considered as sporadic in this review,[15–17,24,28] while the other three reported only MEN1 patients (n = 64).[25–27]

Of the studies reporting sporadic NF-PNETs, all patients were asymptomatic in four of the studies,[15,17,28] 92% in one study,[24] and not disclosed in one study.[16] Of the studies reporting MEN1-related NF-PNETs, all patients were asymptomatic in two studies,[26,27] and 94% in one study.[25]

Characteristics of the tumors

Median size of the sporadic tumors was 10–14 mm (range 3–33 mm), and for MEN1 tumors 5.9–10 mm (range 1.5–24 mm), while not disclosed in detail in one MEN1 study[25] (Table 3). There were multiple tumors in 11 out of 273 patients (4%) with sporadic tumors. One study did not disclose whether patients had single or multiple tumors.[17] Of patients with MEN1-related tumors, 43 out of 64 patients (67%) had multiple tumors.

Table 1 Characteristics of the patients included in studies reporting patients with sporadic NF-PNETs

Study	Selection criteria	Diagnostic work-up	Follow-up protocol
Crippa	Included if: - NF-PNET without malignant features Excluded if: - Distant metastases - Intra-abdominal lymphadenopathy - Infiltration of nearby organs and peripancreatic vessels - Infiltration/obstruction of the main pancreatic duct	CT, MRI, and/or contrast enhanced US. After 1998 all patients underwent somatostatin receptor imaging, which was replaced by gallium-PET after 2007. No FNA confirmation.	Clinicoradiological evaluation every 6 months at 6, 18, 30, 42, and 54 months, and only CT/MRI at 12, 24, 36, 48, and 60 months.
Gaujoux	Included if: - Age over 18 years - Diagnosis of NF-PNET defined by ENETS guidelines - Tumor size smaller than 2 cm on imaging - No pancreatic or bile duct dilation - Sporadic origin - Tumor detected incidentally - No local invasion, node or distant metastasis on imaging - FNA, biopsy or somatostatin receptor imaging confirmed diagnosis - Ki-67 2% or less, if available - No past or present specific treatment of their NF-PNET	CT, MRI, EUS, or nuclear imaging. Confirmation by FNA (21 pts) or SRI (32 pts) in all patients.	Routine outpatient visits at least every 6–12 months with clinical, radiological, and laboratory assessments
Jung	Included if: - Tumor on imaging 2 cm or less - Incidental diagnosis - Asymptomatic and non-functional Excluded if: - Tumor that later turned out not to be PNET - Radiographic signs of local invasion (ductal obstruction, venous thrombosis/narrowing, invasion of adjacent structures, lymph node or distant metastases) - Inherited genetic syndrome (MEN1, VHL) - Follow-up less than 12 months	CT, MRI, or EUS with or without FNA.	Imaging studies (CT or MRI) every 3, 6, or 12 months depending on the size and morphology of the tumors.
Kishi	Included all patients that had been observed for NF-PNET.	Doppler or contrast enhanced US and CT. No routine FNA confirmation.	US or CT at 6-monthly intervals
Lee	Included if: - Primary imaging diagnosis of PNET - Absence of symptoms of pancreatic disease (epigastric pain, jaundice, pancreatitis, symptoms of hormone hypersecretion) Excluded if: - Radiographic sign of local invasion (duct obstruction, venous thrombus/narrowing, invasion of adjacent structures of peripancreatic fat, distant metastases) - Tumor size $\geq$ 4 cm - Familial syndromes associated with PNETs - Known metastases from a non-PNET neoplasm	EUS, CT, or MRI. FNA confirmation in 22 pts. Ki67% in 12 patients.	No standardized protocol provided, patients follow-up using CT, MRI, or EUS.
Sadot	Included if: - A pathological diagnosis or imaging characteristic of PNET - Unambiguous clinic note from the attending surgeon that the stated tumor was PNET Excluded if: - No pathological diagnosis and imaging characteristics also could be another type of tumor	Imaging, but details of work-up not stated. Pathologic tissue diagnosis was obtained in 68 patients (65%). Ki67% not stated.	NS

(*continued on next page*)

Table 1 (*continued*)

Study	Selection criteria	Diagnostic work-up	Follow-up protocol
	- Familial syndrome - Stage III–IV tumor - Largest tumor size over 3 cm in the initial imaging - Age <18 years - Symptomatic or functional PNET as defined by NCCN - Patients were not treatment-naïve - Fewer than two serial cross-sectional imaging studies - Other (non-PNET) stage IV tumor - Fewer than two clinic visits with at least 3 months in between		

Abbreviations: CT – computer tomography, ENETS – European neuroendocrine tumors society, EUS – endoscopic ultrasound, FNA – fine needle aspiration, pts – patients, NCCN – National Comprehensive Cancer Network, NF-PNET – nonfunctional pancreatic neuroendocrine tumor, NS – not stated, MEN1 – multiple endocrine neoplasia type 1, MRI – magnetic resonance imaging, PNET – pancreatic neuroendocrine tumor, SRI – somatostatin receptor imaging, PET – positron emission tomography, US – ultrasound, VHL – Von Hippel-Lindau.

Diagnosis of PNET was confirmed (either by final pathology, fine needle aspiration (FNA), or somatostatin-receptor imaging) in only 152 of 332 patients (46%) with sporadic NF-PNET and 38 of 64 patients (59%) with MEN1 related NF-PNET, while the rest of NF-PNETs were diagnosed by imaging only (endoscopic or abdominal ultrasound, magnetic resonance imaging, and/or computed tomography). For one sporadic NF-PNET study, it was unclear how many diagnoses were confirmed (n = 12),[24] and is not included in the calculations above. Two studies, one with sporadic NF-PNET and the other with MEN1 related NF-PNETs, used either biopsy or somatostatin-receptor imaging in all patients.[15,25]

Tumor growth

Patients with sporadic NF-PNET were followed up to medians ranging from 32 to 45 months with variable follow-up protocols, usually by imaging studies performed approximately 1–2 times a year (Tables 1,3). Five of six studies (n = 267) disclosed the number of patients experiencing tumor growth in follow-up: 84 of 267 patients (range across studies 0–51%, pooled estimate 22% (95% confidence interval 7–41%)) with sporadic NF-PNET had a growing tumor,[15,16,24,28] with considerable heterogeneity (I^2 = 89%) (Table 3, Fig. 2). There was no change in median sporadic tumor size in three studies,[17,24] 0.12 mm or 1.5% (±5.5%) per year in one study,[15] and not disclosed in one study.[16]

Table 2 Characteristic of the patients included in studies reporting patients with MEN1-related NF-PNETs

Study	Selection criteria	Diagnostic work-up	Follow-up protocol
D'Souza	Patients with MEN1 diagnosis undergoing two or more EUS examinations with untreated tumors detected. Nine out of 11 patients had already undergone pancreatic resection or enucleation due to PNET before.	EUS. No FNA confirmation.	EUS yearly, unless patients noncompliant.
Kann	PNETs sized ≤15 mm by EUS without clinical symptoms due to endocrine activity or pancreatic or bile duct obstruction and no clear indication for surgery in patients with MEN1 syndrome. Excluded if therapeutic means were used (somatostatin analogs, alpha-interferon, radioligand therapy, irradiation, embolization, or cytostatic therapy).	EUS + CT or MRI or SRI. No histological verification except for one patient.	EUS scheduled every 6 months, but time interval was on average 9.8 ± 5.1 months.
Partelli	Included if: - NF-PNET in MEN1 syndrome patients Excluded if: - Functional PNET - Size over 2 cm	FNA or somatostatin receptor imaging in all, in addition to EUS and CT.	Variable between centers. All patients underwent at least one CT or MRI yearly. In one center, EUS was performed yearly.

Abbreviations: CT – computer tomography, EUS – endoscopic ultrasound, FNA – fine needle aspiration, NF-PNET – nonfunctional pancreatic neuroendocrine tumor, MEN1 – multiple endocrine neoplasia type 1, MRI – magnetic resonance imaging, PNET – pancreatic neuroendocrine tumor, SRI – somatostatin receptor imaging.

Table 3 Characteristics of NF-PNETs and outcomes of surveillance strategy

Study	n	Tumor size at the beginning of surveillance median (range)	Patients with any tumor growth n (%)	Patients who developed lymph node or distant metastases during follow-up n (%)	Patients who underwent surgery n (%)	Duration of follow-up median (range)
Sporadic tumors						
Crippa	12	14 mm (10–29)	0	0	NS	36 months (18–66)
Gaujoux	46	13 mm (9–15)	12 (26%)	0	8 (17%)	34 months (IQR 24–53)
Jung	85	11–12 mm (4–20)[b]	15 (18%)	NS	12 (14%)	Mean 32 months
Kishi	20[a]	12 mm (6–33)	4 (20%)	0	1 (5%)	45 months (19–162)
Lee	77	10 mm (3–32 mm)	NS	0	2 (3%)	Mean 35 months (3–153)
Sadot	104	12 mm (IQR 8–17 mm)	53 (51%)	0	26 (25%)	44 months (4–223)
MEN1-related tumors						
D'Souza	11	10 mm (5–24)[c]	8 (73%)	NS	6 (55%)	Mean 79 months (18–134)
Kann	20	mean 5.9 mm (1.5–14.5)	NS	0	1 (5%)[e]	20 months (5–45)
Partelli	33	NS, all $\leq$ 20 mm	12 (36%)	5 (15%)[d]	9 (27%)	110 months (IQR 55–157)

Abbreviations: IQR – interquartile range, NS – not stated.
[a] 19 patients in the observation arm plus one patient in the resection arm of the study had a 5-year follow-up in a different hospital, and underwent surgery because PNET size increased from 10 mm to 21 mm. Also includes one patient with Von Hippel-Lindau syndrome. This patient is not included in the patient characteristics.
[b] Size not reported for the whole cohort. Mean size 11 mm for tumors observed for whole follow-up period, and mean 12 mm for tumors that were first observed and then resected in the follow-up.
[c] Reported for 10 out of 11 patients.
[d] Liver metastases in 1 patient, lymph node metastases in 4 patients.
[e] Due to a growing initially larger tumor (20.5 mm) in a patient with also smaller tumors.

Patients with MEN1 related NF-PNET were followed up to medians ranging from 20 to 110 months with variable follow-up protocols (Table 3). Two studies used EUS on 6–12-months interval, while one study used CT, MRI, or EUS once a year (Table 2). Of the two studies that disclosed the number of MEN1 patients experiencing tumor growth, 20 of 44 patients showed tumor growth during follow-up (pooled estimate 52% (95% CI 18–85%), $I^2 = 76\%$)[25,27] (Table 3, Fig. 2). Only one of these two

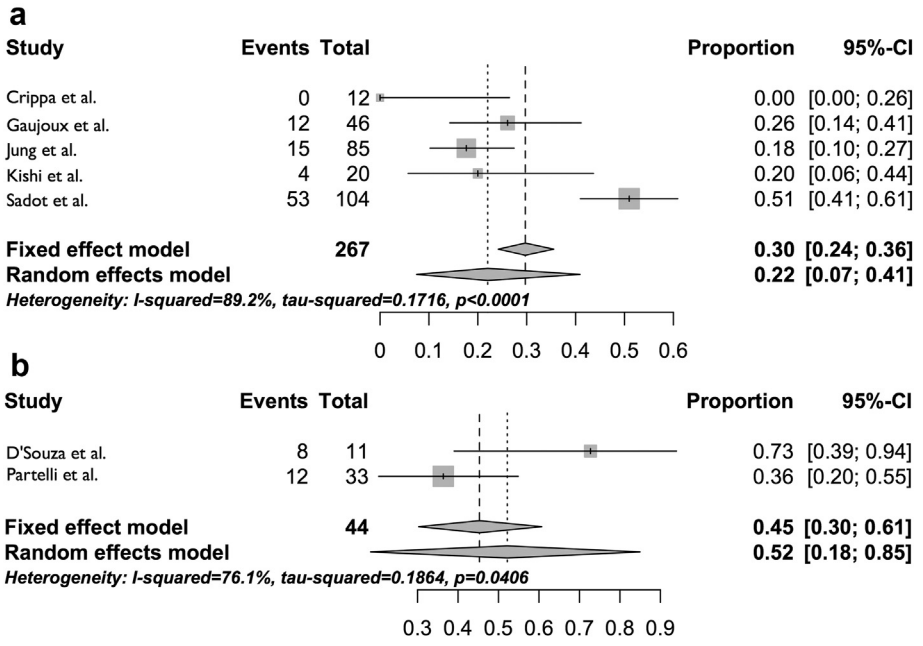

Figure 2 a) Forest plot of proportions of patients with sporadic NF-PNET experiencing tumor growth during follow-up. b) Forest plot of proportions of patients with MEN1 related NF-PNET experiencing tumor growth during follow-up

studies reported growth rate of 0.78 mm (±0.85 mm, range 0–2.52 mm) per year.[27] The third study (n = 20) reported tumor growth of 1.3% (±3.2%, range −7.8% to 10.6%) per month, but not the number of patients experiencing tumor growth.[26]

Development of metastases during follow-up

None of the patients with sporadic NF-PNET developed metastases during the follow-up, while one study did not report data on metastases.[28]

Two of the three studies (n = 53) reported whether patients with MEN1 related NF-PNET developed metastases during follow-up.[25,26] Five of 53 patients (9%) with MEN1 related NF-PNET developed metastases during the follow-up. One patient developed liver metastases, and lymph node metastases were found in four patients who underwent surgery. These five patients were all from one study.[25]

Rate of surgery during follow-up

One study did not disclose the number of patients who underwent surgery during the follow-up (n = 12).[24] Patients undergoing surgical resection after expectant management varied highly from 3% to 25% in studies with sporadic NF-PNETs and from 5% to 55% in studies with MEN1 patients (Table 3). Overall, 49 of 332 patients with sporadic PNET had their tumour resected (pooled estimate 12%, (95% confidence interval 4–23%), I^2 = 83%), while 16 of 64 patients with MEN1 underwent surgical resection (pooled estimate 25% (95% confidence interval 4–54%), I^2 = 80%) (Fig. 3).

Seven studies clearly reported reason for surgery during the follow-up period (n = 59),[15–17,25,26,28] which were as follows: 47% tumor growth (n = 28), 31% patient preference (n = 18), 12% physician preference (n = 7), 3% pancreatic duct dilation (n = 2), 3% development of new lesions (n = 2), development of symptoms (n = 1) and 2% unknown (n = 1). Two studies reported the grade of the resected tumors (20 resected of 131 patients),[15,28] which were grade 1 in 18 patients and grade 2 in two patients. Overall, eight of the nine studies favor expectant management for small asymptomatic NF-PNETs, while one with MEN1 patients recommends an individualized approach.[27]

Discussion

In view of the significant morbidity of pancreatic surgery, and the indolent natural history of at least a subset of small (≤2 cm), asymptomatic, and nonfunctional PNETs, systematic surgery is controversial.

This systematic review of expectant management of small asymptomatic NF-PNETs found that sporadic NF-PNETs have low rate of tumor growth (22%), need for secondary surgical resection (12%), and very low rate of disseminated disease in follow-up (0%). On the contrary, patients with MEN1 related NF-PNETs appear to have higher rates of tumor growth (52%), need for surgical resection (25%), and rate of disseminated disease (9%), but these results should be interpreted with caution, because of the longer and specific follow-up of this subgroup of patients. In light of these results, despite the lack of high

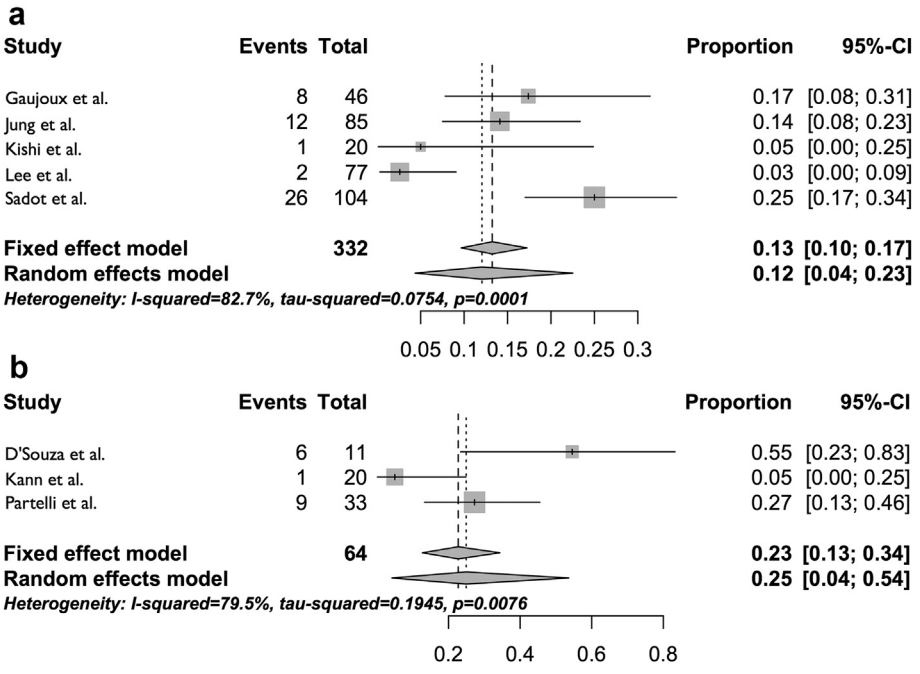

Figure 3 a) Forest plot of proportions of patients with sporadic NF-PNET undergoing tumor resection in follow-up. b) Forest plot of proportions of patients with MEN1 related NF-PNET undergoing tumor resection in follow-up

quality studies and the retrospective nature of published ones, expectant management in highly selected patients with sporadic small (≤2 cm), asymptomatic NF-PNETs could be a safe option.

Routine resection of all neuroendocrine lesions of the pancreas has long been advocated. With substantial progress in the knowledge of the natural history of sporadic or MEN 1 small (≤2 cm), asymptomatic, and NF-PNETs a more selective approach to resection is proposed as suggested in various recommendations.[19–21] However, this surveillance strategy remains controversial,[9,18] because of the risk of metastatic progression during follow-up. The optimal cut-off size to proceed to up-front surgical resection is also controversial and varies between 1 and 2 cm.[19–21,28] In the present study, 9% of patients with MEN1 syndrome developed nodal or distant metastases during their follow-up. This is in accordance with previous cohort studies.[29] Even if duodenopancreatic tumors including NF-PNETs increase the risk of death,[30] this should be balanced by the significant postoperative morbidity and mortality of pancreatic surgery. Postoperative mortality is often reported around 1% in high-volume centers,[31–33] but increases up to 10% when nationwide data is considered.[34] Of course, age, comorbidities, and location of the tumor affects the morbidity and mortality rates and different strategies need to be employed in tumors located in the distal pancreas compared to tumors requiring pancreaticoduodenectomy. On the other hand, sporadic NF-PNETs did not develop disseminated disease in follow-up albeit 12% of tumors showed growth suggesting a possibility for surveillance strategy, especially for tumors located in the head of pancreas. Whether MEN1 and sporadic NF-PNETs harbor different biological behavior remains to be formally clinically and scientifically demonstrated.

In contrary to these results, two recent large registry studies based on the analysis of the US National Cancer Data Base (NCDB) reported that small (≤2 cm) NF-PNETs have malignant potential and that survival significantly improved in patients that underwent surgical resection compared to the observation arm.[11,12] After excluding patients with metastases, comorbidities excluding surgery, and death before surgery, one of the studies demonstrated an unadjusted 5-year overall survival for patients with small (≤2 cm) NF-PNET undergoing observation 28% compared to patients undergoing oncological surgical resection 72–86%.[11] The other study reported a median 5-year overall survival for patients with small NF-PNET undergoing observation 34% compared to 82% overall survival in patients with surgery.[12] Both studies conclude that all small NF-PNETs should be resected. These findings are in great contrast to studies included in this systematic review. Several reasons for this discrepancy can be found. First, and perhaps most importantly, both reports, being registry-based studies, lack reporting the reason for surveillance in these patients. It is of note that patients who underwent surgical resection had private insurance more often than patients undergoing observation,[12] which might affect decision-making. Secondly, they do not disclose whether these tumors were symptomatic and if they caused bile or pancreatic duct dilation. These obstructions are known factors correlating to aggressive behavior of small NF-PNETs, and such patients are not recommended to undergo expectant management.[14,35] Thirdly, observation groups in neither of these reports are truly observative, since 9–21% patients received chemo- and/or radiotherapy.[11,12] Lastly, it is likely that in a clinical oncology database, because of inclusion bias, patients with less aggressive tumors are underrepresented. Neither of these studies were included in this systematic review, because characteristic of patients undergoing observation are not clearly reported and patients received oncological therapies. However, selection bias could also be a problem in this review since diagnosis was only confirmed in 48% of the patients.

Several publications reporting outcomes after resection for small asymptomatic NF-PNETs exist. In the largest series, Haynes *et al.* (2011) reported that 3 of 39 patients (8%) with asymptomatic, small NF-PNET that had undergone surgical resection developed metastases and died of disease after a median follow-up of 34 months. In another report, 16 small asymptomatic NF-PNETs patients were followed for median 27 months.[14] One of the asymptomatic patients had lymph node metastases, but none of them developed distant metastases or died of disease. Birnbaum *et al.* (2014) reported that three of 34 patients (9%) with resected asymptomatic, small (≤2 cm) NF-PNETs had lymph node metastases.[35] In light of these results, it seems evident that patients selected for surgery have lymph node metastases more frequently than patients who undergo expectant management. Parameters, which should be used to select patients for expectant management or surgery in this context, are unclear. Moreover, there is underestimation of lymph node positivity detected via CT,[36] another issue to keep in mind in selecting treatment option.

How to best select patients with a NF-PNET for surgery remain controversial. Size of course should be the first criteria, but whether a 10 mm,[21] 15 mm,[28] 17 mm,{Regenet:2015ki} or 20 mm[15] cut-off should be used remains to be clearly identified. In our opinion the cut-off size should be balanced with i) patients' comorbidity and risk of postoperative death,[37] ii) life expectancy, iii) tumor location (pancreaticoduodenectomy carries a higher risk than distal resection), iv) risk of postoperative pancreatic fistula[38,39] and postoperative morbidity,[40,41] and v) possibly in a near future tumor genetic alteration.[42,43]

If surgery is advocated, careful consideration of the magnitude of operation is needed, and parenchyma sparing procedure should be preferred. Enucleation is a possibility in small NF-PNETs distant (at least 2 mm) from the main pancreatic duct without signs of malignancy.[44] Central pancreatectomy is another option for parenchyma preserving pancreatectomy if the tumor is close to the main pancreatic duct. Both of these parenchyma preserving pancreatectomies have the advantage of preserving endo- and exocrine function in the long term, but the downside is increased risk of pancreatic fistula and higher rate of R1-resections.[14,45–47]

If surveillance strategy is chosen, no strong recommendation regarding the interval and imaging modality can be stated. Most of the studies used CT, MRI, or US at 6–12 months interval. US might be sufficient to detect growth of the tumour, but insufficient in detecting lymphadenopathy and distant lesions, which is crucial. CT and MRI are likely comparable, but CT has the disadvantage of radiation exposure, which might be significant as patients could be under surveillance for years. In our opinion, first imaging should be done 3 months after detecting the tumor, and can then be gradually lengthened to 6–12 months if no growth is seen.

If a watchful strategy could be reasonable in sporadic small, asymptomatic, and non-functional PNETs, it is unclear whether this applies for MEN1 patients. Pancreatic surgery is likely to be more challenging because of multiple lesions and risk for the need of total pancreatectomy if considerable. Thus, how to best select MEN1 patients for surgery based on age, cut-off size, and/or location remains to be formally determined.[48]

There are several limitations in this systematic review and in the included studies. First, only nine studies were found to meet the criteria for this systematic review. Although there are other reports of expectant management of small NF-PNETs, they failed to disclose necessary details or reported only a few patients. Furthermore, the included nine studies investigated only 408 patients in total. The fact that such a low number of patients were treated in fourteen centers over study periods from 11 to 32 years demonstrate the rarity of the disease and the difficulty to study it. Despite the long study periods, the follow-up periods were relatively short spanning 2–4 years in most studies. Moreover, there seemed to be substantial publications bias and high heterogeneity between the studies. This suggests that, for a rare disease, good responders or successful strategies are selected over poor outcomes. While surveillance seemed safe in the sporadic patient populations, these results should be interpreted with caution as patients in these cohorts are highly selected. Results from larger prospective multicenter trials are needed, but are unlikely available in a close future.

In conclusion, despite scarce literature with low level of evidence, expectant management of highly selected sporadic small asymptomatic NF-PNETs seems safe. These results should be interpreted with caution as the underlying studies are small retrospective series with only a short follow-up. How to best select patient for surveillance strategy (age, cut-off size, tumor location, imaging features) remains to be clearly determined, and studies with longer follow-up are needed.

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Conflicts of interest

Authors declare no conflict of interest.

References

1. Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY *et al*. (2008) Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors. *Ann Surg* 247:490–500.
2. Ellison TA, Wolfgang CL, Shi C, Cameron JL, Murakami P, Mun LJ *et al*. (2014) A single institution's 26-year experience with nonfunctional pancreatic neuroendocrine tumors. *Ann Surg* 259:204–212.
3. Hashim YM, Trinkaus KM, Linehan DC, Strasberg SS, Fields RC, Cao D *et al*. (2014) Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). *Ann Surg* 259: 197–203.
4. Kim MJ, Choi DW, Choi SH, Heo JS, Park HJ, Choi KK *et al*. (2012) Surgical strategies for non-functioning pancreatic neuroendocrine tumours. *Br J Surg* 99:1562–1568.
5. Fischer L, Bergmann F, Schimmack S, Hinz U, Prieß S, Müller-Stich BP *et al*. (2014) Outcome of surgery for pancreatic neuroendocrine neoplasms. *Br J Surg* 101:1405–1412.
6. Hayward R. (2003) Personal view: VOMIT (victims of modern imaging technology)—an acronym for our times. *BMJ* 326:1273.
7. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE *et al*. (2008) One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 26:3063–3072.
8. Bilimoria KY, Tomlinson JS, Merkow RP, Stewart AK, Ko CY, Talamonti MS *et al*. (2007) Clinicopathologic features and treatment trends of pancreatic neuroendocrine tumors: analysis of 9821 patients. *J Gastrointest Surg* 11:1460–1469.
9. Janson ET, Sorbye H, Welin S, Federspiel B, Grønbæk H, Hellman P *et al*. (2014) Nordic guidelines 2014 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. *Acta Oncol* 53:1284–1297.
10. Falconi M, Pl ouml ckinger U, Kwekkeboom DJ, Manfredi R, Koumlrner M, Kvols L *et al*. (2006) Well-differentiated pancreatic nonfunctioning tumors/carcinoma. *Neuroendocrinology* 84:196–211.
11. Gratian L, Pura J, Dinan M, Roman S, Reed S, Sosa JA. (2014) Impact of extent of surgery on survival in patients with small nonfunctional pancreatic neuroendocrine tumors in the United States. *Ann Surg Oncol* 21:3515–3521.
12. Sharpe SM, In H, Winchester DJ, Talamonti MS, Baker MS. (2014) Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. *J Gastrointest Surg* 19:117–123.
13. Haynes AB, Deshpande V, Ingkakul T, Vagefi PA, Szymonifka J, Thayer SP *et al*. (2011) Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. *Arch Surg* 146:534–538.
14. Sallinen V, Haglund C, Seppänen H. (2015) Outcomes of resected nonfunctional pancreatic neuroendocrine tumors: do size and symptoms matter? *Surgery* 158:1556–1563.
15. Gaujoux S, Partelli S, Maire F, D'Onofrio M, Larroque B, Tamburrino D *et al*. (2013) Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab* 98:4784–4789.

16. Kishi Y, Shimada K, Nara S, Esaki M, Hiraoka N, Kosuge T. (2014) Basing treatment strategy for non-functional pancreatic neuroendocrine tumors on tumor size. *Ann Surg Oncol* 21:2882–2888.
17. Lee LC, Grant CS, Salomao DR, Fletcher JG, Takahashi N, Fidler JL *et al*. (2012) Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): role for nonoperative management. *Surgery* 152:965–974.
18. Oberg K, Knigge U, Kwekkeboom D Perren A, &, ESMO Guidelines Working Group. (2012) Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, (Suppl. 7):vii124–vii130.
19. Falconi M, Bartsch DK, Eriksson B, Klöppel G, Lopes JM, O'Connor JM *et al*. (2012) ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology* 95:120–134.
20. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M *et al*. (2016) ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology* 103: 153–171.
21. Kulke MH, Shah MH, Benson AB, Bergsland E, Berlin JD, Blaszkowsky LS *et al*. (2015) Neuroendocrine tumors, version 1.2015. *JNCCN* 13:78–108.
22. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 73:712–716.
23. Panic N, Leoncini E, de Belvis G, Ricciardi W, Boccia S. (2013) Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS One* 8:e83138.
24. Crippa S, Partelli S, Zamboni G, Scarpa A, Tamburrino D, Bassi C *et al*. (2014) Incidental diagnosis as prognostic factor in different tumor stages of nonfunctioning pancreatic endocrine tumors. *Surgery* 155: 145–153.
25. Partelli S, Tamburrino D, Lopez C, Albers M, Milanetto AC, Pasquali C *et al*. (2016) Active surveillance versus surgery of nonfunctioning pancreatic neuroendocrine neoplasms $\leq$2 cm in MEN1 patients. *Neuroendocrinology* 103:779–786.
26. Kann PH, Balakina E, Ivan D, Bartsch DK, Meyer S, Klose K-J *et al*. (2006) Natural course of small, asymptomatic neuroendocrine pancreatic tumours in multiple endocrine neoplasia type 1: an endoscopic ultrasound imaging study. *Endocr Relat Cancer* 13:1195–1202.
27. D'souza SL, Elmunzer BJ, Scheiman JM. (2014) Long-term follow-up of asymptomatic pancreatic neuroendocrine tumors in multiple endocrine neoplasia type I syndrome. *J Clin Gastroenterol* 48:458–461.
28. Jung JG, Lee KT, Woo YS, Lee JK, Lee KH, Jang K-T *et al*. (2015) Behavior of small, asymptomatic, nonfunctioning pancreatic neuroendocrine tumors (NF-PNETs). *Medicine* 94:e983.
29. Triponez F, Dosseh D, Goudet P, Cougard P, Bauters C, Murat A *et al*. (2006) Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. *Ann Surg* 243: 265–272.
30. Goudet P, Murat A, Binquet C, Cardot-Bauters C, Costa A, Ruszniewski P *et al*. (2010) Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. *World J Surg* 34:249–255.
31. Cameron JL, He J. (2015) Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 220:530–536.
32. Winter JM, Brennan MF, Tang LH, D'Angelica MI, DeMatteo RP, Fong Y *et al*. (2012) Survival after resection of pancreatic adenocarcinoma: results from a single institution over three decades. *Ann Surg Oncol* 19: 169–175.
33. Pugalenthi A, Protic M, Gönen M, Kingham TP, Angelica MID, DeMatteo RP *et al*. (2016) Postoperative complications and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. *J Surg Oncol* 113:188–193.
34. Nimptsch U, Krautz C, Weber GF, Mansky T, Grützmann R. (2016) Nationwide in-hospital mortality following pancreatic surgery in Germany is higher than anticipated. *Ann Surg* 264:1082–1090.
35. Birnbaum DJ, Gaujoux S, Cherif R, Dokmak S, Fuks D, Couvelard A *et al*. (2014) Sporadic nonfunctioning pancreatic neuroendocrine tumors: prognostic significance of incidental diagnosis. *Surgery* 155: 13–21.
36. Takumi K, Fukukura Y, Higashi M, Ideue J, Umanodan T, Hakamada H *et al*. (2015) Pancreatic neuroendocrine tumors: correlation between the contrast-enhanced computed tomography features and the pathological tumor grade. *Eur J Radiol* 84:1436–1443.
37. Dias-Santos D, Ferrone CR, Zheng H, Lillemoe KD, Fernández-del Castillo C. (2015) The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer. *Surgery* 157:881–887.
38. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM. (2013) A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg* 216: 1–14.
39. Jiang H, Liu N, Zhang M, Lu L, Dou R, Qu L. (2016) A randomized trial on the efficacy of prophylactic active drainage in prevention of complications after pancreaticoduodenectomy. *Scand J Surg* 105:215–222.
40. Kneuertz PJ, Pitt HA, Bilimoria KY, Smiley JP, Cohen ME, Ko CY *et al*. (2012) Risk of morbidity and mortality following hepato-pancreato-biliary surgery. *J Gastrointest Surg* 16:1727–1735.
41. Ansari D, Tingstedt B, Lindell G, Keussen I, Andersson R. (2016) Hemorrhage after major pancreatic resection: incidence, risk factors, management, and outcome. *Scand J Surg*. Feb 29 (Epub ahead of print).
42. Marinoni I, Kurrer AS, Vassella E, Dettmer M, Rudolph T, Banz V *et al*. (2014) Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. *Gastroenterology* 146:453–455.
43. Haugvik S-P, Vodák D, Haugom L, Hovig E, Gladhaug IP, Heim S *et al*. (2016) Transcriptomic profiling of tumor aggressiveness in sporadic nonfunctioning pancreatic neuroendocrine neoplasms. *Pancreas* 45: 1196–1203.
44. Brient C, Regenet N, Sulpice L, Brunaud L, Mucci-Hennekine S, Carrere N *et al*. (2012) Risk factors for postoperative pancreatic fistulization subsequent to enucleation. *J Gastrointest Surg* 16: 1883–1887.
45. Jilesen APJ, van Eijck CHJ, in't Hof KH, van Dieren S, Gouma DJ, van Dijkum EJMN. (2016) Postoperative complications, in-hospital mortality and 5-year survival after surgical resection for patients with a pancreatic neuroendocrine tumor: a systematic review. *World J Surg* 40:729–748.
46. Jilesen APJ, van Eijck CHJ, Busch ORC, van Gulik TM, Gouma DJ, van Dijkum EJMN. (2016) Postoperative outcomes of enucleation and

standard resections in patients with a pancreatic neuroendocrine tumor. *World J Surg* 40:715–728.

47. Cherif R, Gaujoux S, Couvelard A, Dokmak S, Vuillerme M-P, Ruszniewski P *et al*. (2012) Parenchyma-sparing resections for pancreatic neuroendocrine tumors. *J Gastrointest Surg* 16:2045–2055.

48. Cucchetti A, Ricci C, Ercolani G, Campana D, Cescon M, D'Ambra M *et al*. (2015) Efficacy and cost-effectiveness of immediate surgery versus a wait-and-see strategy for sporadic nonfunctioning T1 pancreatic endocrine neoplasms. *Neuroendocrinology* 101:25–34.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2016.12.010.