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Management and surveillance of non-functional pancreatic neuroendocrine tumours: Retrospective review

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ABSTRACT

Background: /Objective. To determine the outcomes of a non-operative management approach for sporadic, small, non-functional pancreatic neuroendocrine tumours.
Methods: A retrospective chart review of patients with non-functional pancreatic neuroendocrine tumours initially managed non-operatively at a single institution was performed. Patients were identified through a search of radiologic reports, and individuals with ≥2 cross-sectional imaging studies performed >6 months apart from Jan. 1, 2000 to Dec. 31, 2013 were included. Data on tumour size, radiologic characteristics at diagnosis, interval radiologic growth, and surgical outcomes were recorded.
Results: Over the thirteen-year study period, 95 patients met inclusion criteria and were followed radiologically for a median of 36 months (18–69 months). Median initial tumour size on first imaging was 14.0 mm (IQR 10–19 mm). Median overall tumour growth rate was 0.03 mm/month (IQR: 0.00 −0.14 mm/month). There was no significant relationship between initial tumour size and growth rate for tumours ≤ 2 cm or for lesions between 2 and 4 cm. Thirteen (14%) patients initially managed non-operatively underwent resection during the follow-up period. Reasons for surgery included interval tumour growth, patient anxiety or preference, or diagnostic uncertainty. Median time to surgery was 14 months (IQR 8–19 months). No patients progressed beyond resectability or developed metastatic disease during the observation period.
Conclusion: For patients with sporadic, small, non-functional pancreatic neuroendocrine tumours, radiologic surveillance appears to be a safe initial approach to management.

Introduction

Pancreatic neuroendocrine tumours (PNETs) describe a group of diverse neoplasms that arise from progenitor islet cells and account for 1–2% of pancreatic neoplasms. They are classified as functional and non-functional, depending on their ability to secrete biologically active hormones [1]. Functional tumours are typically treated with resection or medical management for symptomatic relief. Non-functional sporadic PNETs account for half of all PNETs and are increasingly diagnosed as an incidental finding due to increasing frequency of high quality cross-sectional imaging [2]. The management of non-functional PNETs is highly variable. Challenges arise in the management of these tumors because of their unpredictable biological behavior and wide range of aggressiveness in their clinical course [3].

The majority of non-functional PNETs are slow-growing and

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indolent; however, some may display malignant potential and aggressive behaviour. In view of this, 5- year survival can range from 25 to 100% [4]. This heterogeneity in their clinical course makes standardization of management and surveillance challenging. There is emerging data on active radiologic surveillance of PNETs with varying criteria for observation based on the size of the lesion. Guidelines set forth by the European Neuroendocrine Tumor Society in 2012 state that it is reasonable to observe some non-functional, small (<2 cm) lesions [1]. Guidelines by the National Comprehensive Cancer Network also state that observation may be safe for lesions <1 cm and resection should be considered in those lesions >2 cm in the absence of contraindications to surgery [5].

Our primary study objective was to determine the safety of non-operative management for small, asymptomatic, sporadic, non-functional PNETs by investigating the relationship between tumour size at diagnosis and growth rate over the surveillance period. The secondary objectives were to analyze the risk of malignant progression and to explore the association between patient characteristics and tumour growth.

Materials and methods

Patient selection

We performed a retrospective review of a clinical radiologic database at the University Health Network (UHN)-Toronto General Hospital (a tertiary referral centre in Toronto, Ontario, Canada) that included patients from January 1, 2000 to December 31, 2013. The study protocol was approved by the research ethics board at the UHN. We searched reports of abdominal imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) using search terms determined *a priori* (PNETs, pancreatic neuroendocrine tumours of the pancreas) to identify patients with PNETs.

Patients with tumors displaying the characteristic appearance of PNET (hypervascular, arterially enhancing, well circumscribed lesion) as determined by the radiologist and who did not undergo upfront resection (determined based on subsequent imaging) were selected for study inclusion. Patients who underwent ≥2 abdominal imaging studies over a time period of >6 months and were seen in consultation by a hepato-pancreato-biliary (HPB) surgeon with a documented clinical decision for radiologic observation were included. Verification of appointment with a HPB surgeon was confirmed based on initial consultation note. Patients with tumours suspicious for malignancy at the time of diagnosis were excluded (suspicious findings included heterogeneity on imaging, calcifications, pancreatic ductal dilatation, questionable nodal enlargement, or metastatic disease). Additional exclusion criteria on chart review included patients with symptoms of pancreatic endocrine excess syndromes (flushing, abdominal pain, palpitations, diarrhea), functional tumours (evidence of hormone production either based on symptoms, or biochemical testing), and familial syndromes (including multiple endocrine neoplasia syndrome type I (MEN1), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF-1), and tuberous sclerosis (TSC).

Electronic medical records (EMR) were searched to obtain demographic, clinical and follow-up data. Pathology reports were also obtained from the EMR for those patients who underwent resection. The World Health Organization (WHO) staging system was utilized to grade tumours; G1 was used to describe well differentiated, low grade tumours (<2 mitoses/10 HPF and no necrosis), G2 described well differentiated, intermediate grade (2–10 mitoses/HPF and/or foci of necrosis) tumours, and G3 described poorly differentiated, high grade (>20 mitoses per HPF) tumours.

Data extraction

We used a standardized data extraction form to extract patient characteristics and follow-up information, including patient age, sex, size of tumour on first available imaging study, and date of resection or reason for ongoing surveillance, where relevant. For each radiologic study recorded for each patient, radiologic reports were used to extract date of imaging, modality, and tumour size. Follow-up time was calculated as the time, in months, from the first to the last recorded imaging study. For patients who underwent resection, we searched operative and surgical pathology reports to determine tumour size and histology at surgical resection.

Outcomes

The primary outcome was overall tumour growth rate (mm/month). Tumour growth was defined as the difference in tumour size (in mm) between first and last imaging study.

Statistical analysis

Baseline patient characteristics, follow-up time, initial tumour size, number of imaging studies per patient, and overall tumour growth rate were tested for normality using the Shapiro-Wilk test and, due to non-normality, these measures are presented as median and interquartile range (IQR). To evaluate the study question of whether initial tumour size was associated with overall tumour growth rate, we assessed for correlations between overall tumour growth rate and initial tumour size using the Spearman correlation coefficient. We separately evaluated the characteristics of patients who underwent resection during the follow-up period, including surgical pathology findings, to investigate trends in growth patterns among these patients.

Statistical analysis was performed using SAS® Studio v.3.5 (SAS Institute Inc., Cary, NC, USA). All tests were two-sided with a p-value < 0.05 considered statistically significant.

Results

Patient characteristics

We identified 95 patients within our database with a radiologic diagnosis of PNET that met inclusion criteria (Fig. 1). Patient

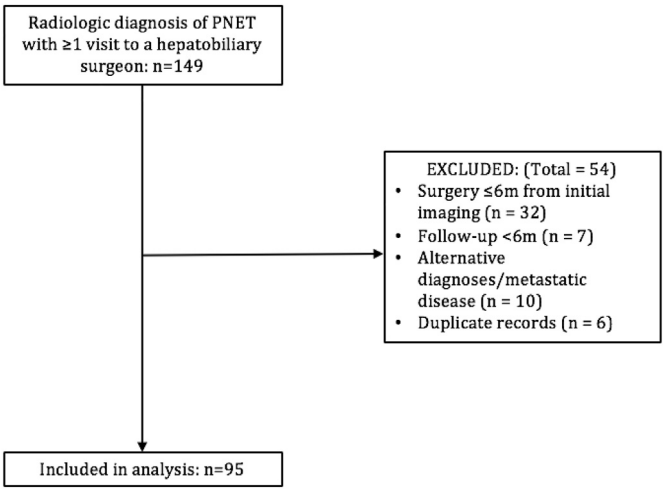

Fig. 1. STROBE flow diagram of cohort detailing cohort creation.

Table 1
Patient, tumour, and treatment characteristics. All continuous variables reported as median (IQR).

Patient and follow up characteristics (n=95)	
Sex, % (M,F)	42, 58
Age at first imaging, *years*	60 (50–71)
Initial tumour size, *mm*	14.0 (10–19)
Number of imaging studies	6 (4–9)
Follow up time, *months*	36 (18–69)
Interval growth, *mm/month*	0.03 (0.00–0.14)
Resected during follow-up, %	13,13.6%

characteristics are described in Table 1. The median age of patients was 60 years (IQR 50–71 years); 42% of patients were male. Median initial tumour size on first imaging was 14.0 mm (IQR 10–19 mm). Median follow up time was 36 months (IQR 18–69 months). Over the study period, 13 patients underwent surgical resection.

Overall tumour growth

Tumour size and rate of change were evaluated over the length of each patient's follow-up period. Median overall tumour growth rate was 0.03 mm/month (IQR: 0.00–0.14 mm/month) or 0.30 mm/year (IQR: 0–1.5 mm/year). Four patients had tumours that reached > 2 cm during the follow-up period and a decision was made to continue non-operative management secondary to comorbid disease or patient preference to avoid surgery. On examination of the overall tumour growth rate as a function of initial tumour size, there was no appreciable relationship between initial tumour size and growth rate for tumours ≤2 cm (Spearman $\rho = -0.07$; Fig. 2a) or for tumours 2–4 cm (Spearman $\rho = 0.30$; $n = 16$; Fig. 2b). When initial and final tumour size were plotted separately for each patient throughout their follow-up period, the majority ($n = 80$) of patients managed non-operatively did not demonstrate any significant increase in tumour size over the observation period, though a small number of tumours demonstrated erratic growth patterns (Fig. 3). Of note, none of the patients who were followed radiographically developed metastatic disease or progressed beyond resectability during their surveillance period.

Growth in resected patients

Thirteen of the 95 patients initially managed non-operatively underwent surgical resection during the follow-up period (Table 2). Reasons for surgery included interval tumour growth ($n = 5$), patient anxiety ($n = 2$), patient preference ($n = 2$), or diagnostic uncertainty ($n = 4$). Median time to surgery was 14 months (IQR: 8–19 months). Surgical pathology confirmed the diagnosis of PNET in 11 (85%) patients; 5 (38%) patients demonstrated grade I lesions and 6 (46%) demonstrated grade II tumours. Two (15%) patients were found to have alternate diagnoses (pseudopapillary neoplasm and lymphoma). There was a median discrepancy of 2.6 mm between last radiologic size and pathologic tumour size (range 0–5.0 mm). Interval tumour growth was examined as a function of follow-up time in each patient. Patients who ultimately underwent surgical resection did not demonstrate predictable monthly increases in tumour size (Fig. 4).

Discussion

Our retrospective analysis of 95 patients with non-functional PNETs initially managed non-operatively demonstrates that few of these tumours have erratic growth patterns and most grow slowly, allowing for a non-operative management strategy with frequent surveillance to be undertaken. Over a median 36-month observation period, only 5 patients underwent resection due to interval tumour growth. No patients in our cohort who were managed non-operatively developed unresectable or metastatic disease during the follow-up period. None of the 13 patients who underwent surgical resection demonstrated features of advanced disease on final pathological assessment.

Pancreatic neuroendocrine tumours are a group of heterogeneous tumours with respect to their biologic behaviour and potential for malignant progression. While the literature strongly supports surgical resection of functional PNETs (stage I-III and some stage IV [6]) for the relief of symptoms and oncologic cure [7], the surgical management of non-functional, sporadic PNETs remains controversial [8,9]. As suggested by the WHO staging, many small PNETs may have less aggressive features and may exhibit an indolent natural history [3,10,11]. With increasing frequency of

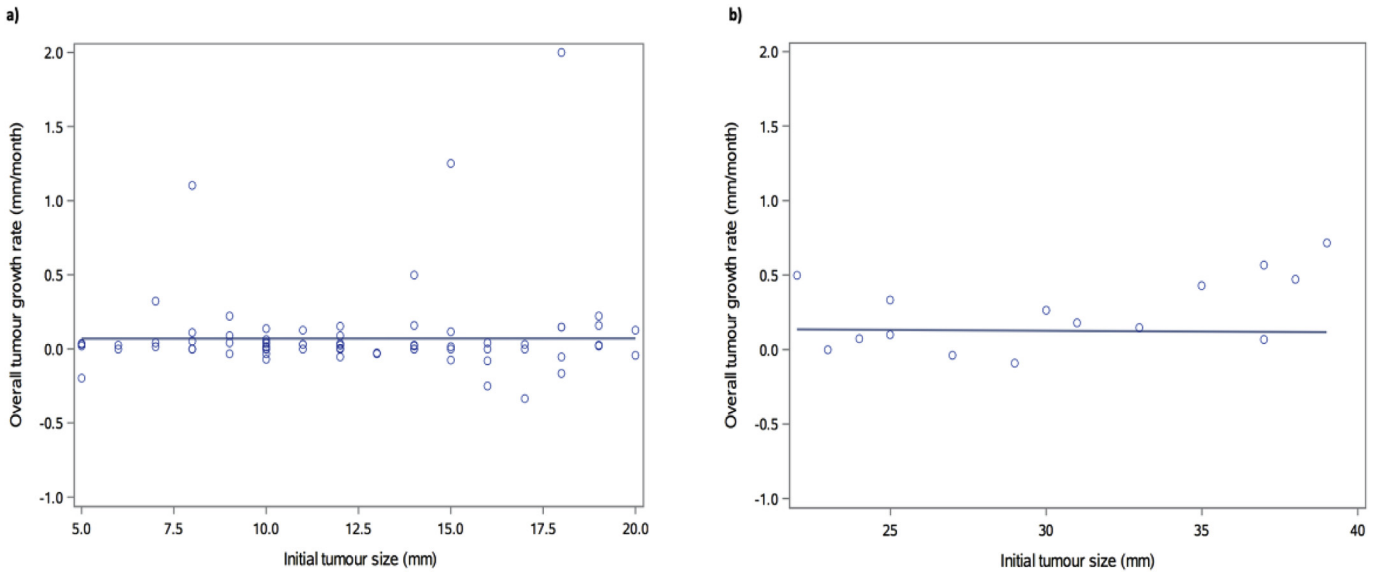

Fig. 2. Overall tumour growth (mm/month) based on initial tumour size (mm) in patients. a) initial tumour size ≤2 cm, b) initial tumour size 2–4 cm.

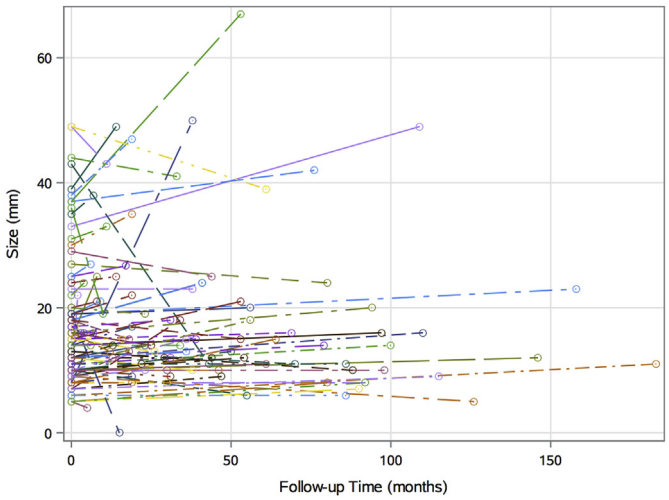

Fig. 3. . Initial and final tumour size by follow-up time for all patients. Each line represents a single patient. Although few patients demonstrated erratic growth patterns, most patients did not exhibit any appreciable tumour growth during the follow-up period.

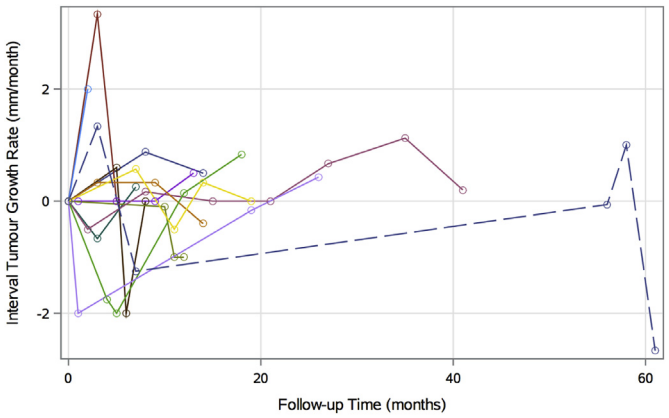

Fig. 4. Interval tumour growth (mm/month) by follow-up time for resected patients. Each line represents a single patient. There were no predictable growth patterns seen among resected patients.

radiologic imaging studies being performed on a population level, the rising incidental detection of non-functional PNETs has resulted in a need for high-level evidence guidelines to direct safe management of these tumours [4,12,13].

Several retrospective studies have evaluated the role for conservative management of sporadic, non-functional PNETs [10,14–19] [Table 3: also compares patients who were resected]. These studies have shown that lesions < 2 cm exhibit lower pathologic grade, no evidence of local invasion, slow tumor growth, and are not associated with metastatic disease or disease-specific mortality [15,18]. In a review of 133 patients, 77 patients showed no evidence of significant tumor growth on serial imaging for patients who underwent observation over a period of 45 months [18]. Similarly, Jung et al. [20] recently published an observational study of 145 patients depicting similar findings in the same subset of patients, also concluding that older age (>55 years), larger tumour size (>15 mm) and meaningful tumour growth (≥20% or ≥ 5 mm over 31.1±22.1 months) were associated with grade II/III lesions. A retrospective analysis by Sillinen and colleagues looked at patients with small, non-functional PNETs who underewent resection across 16 centres to identify factors associated with recurrence. Tumor size, presence of biliary or pancreatic duct dilatation on preoperative imaging and WHO grade 2–3 were independently associated with recurrence. All patients with tumors </= 10 mm were disease free at 1-, 3- and 5- year follow up and as tumor size increased survival was worse [21]. These findings are consistent with the results of our study. Importantly, these studies have also highlighted a >40% complication rate associated with pancreatic resection [18], suggesting that the oncological risks of observation should be balanced against the high risk of surgery. Several meta-analyses also support the findings of our study. A meta-analysis performed by Bettini et al. [22] showed that size of the lesion was associated with malignant potential and should be considered when determining the most appropriate management strategy. In this study, tumours >20 mm and non-incidental tumours were independent predictors of malignancy; however, tumours ≤20 mm were most often incidentally discovered. In another recent systematic review [17], which included five retrospective studies (n = 540), 46 of 327 patients initially managed non-operatively underwent surgical resection during the follow-up period. Only 19 of these patients underwent resection due to increases in tumour size. There were no disease-related deaths in the active surveillance groups, furthering supporting the safety of close radiologic surveillance for these patients. Similarly, a systematic review and meta-analyses by Sallinen and colleagues [23] evaluated nine studies looking at surveillance of patients with sporadic, non-functional PNETS. A total of 344 patients with sporadic and 4 patients with MEN1-related PNETs were analyzed. The authors observed tumour growth in 22% and 52% of the patients, respectively, with metastases of 9% in patients with MEN1-related tumours; the rate of secondary surgical resection was 12% and 25% in patients with sporadic or MEN1 related PNETs, respectively. All metastases (1 distant, 4 nodal) were reported by a single study in

Table 2
Characteristics of patients who underwent resection after being allocated to a watch and wait strategy.

Patient	Sex	Follow up time	Age at resection	Initial tumour size	Tumour size prior to resection	Tumour size at surgery	Pathology
1	F	14	69	49	39	44	Grade I NET
2	F	8	65	15	25	20	Lymphoma
3	F	3	67	17	16	15	Grade I NET
4	F	8	64	20	21	20	Grade II NET
5	M	13	36	12	14	12	Grade I NET
6	F	12	35	16	13	13	Grade II NET
7	F	2	37	18	22	24	Solid pseudopapillary neoplasm
8	F	41	62	18	24	21	Grade II NET
9	F	14	69	24	25	20	Grade II NET
10	M	18	47	18	15	13	Grade I NET
11	M	26	77	15	13	15	Grade II NET
12	F	19	54	19	22	23	Grade I NET
13	F	61	53	49	39	44	Grade II NET

Table 3
Summary of literature regarding surveillance of pancreatic neuroendocrine tumors.

Author	Year	Type of study	Number of patients, patients who underwent surgery	Findings (range)
Gaujoux [15] et al.	2013	Observation vs. surgery	46, 8	Median follow-up of 34 months (24–52) Average imaging sessions: 4 (3–6), distant or nodal metastases appeared on the imaging in none of the patients. In six patients (13%), a 20% or greater increase in size was observed. Overall median tumor growth was 0.12 mm per year, and neither patients nor tumor characteristics were found to be significant predictors of tumor growth. Eight patients (17%) underwent surgery after a median time from initial evaluation of 41 months (range 27–58); all resected lesions were European Neuroendocrine Tumor Society T stage 1 (n = 7) or 2 (n = 1), grade 1, node negative, with neither vascular nor peripancreatic fat invasion.
Lee [18] et al.	2012	Observation vs. surgery	133, 56	**Non operative patients: n = 77** Median tumor size: 1 cm (0.3–3.2), Mean follow up was 45 months. Median tumor size did not change throughout f/u period. No disease progression, no disease specific mortality. **Operative patients: n = 56** Median size 1.8 cm (0.5–3.6), mean f/u was 52 months (max 138 months). 46% of patients had postoperative complications, >1/2 due to pancreatic leak. No recurrence or disease specific mortality, 5 patients with + lymph nodes
Jung [20] et al.	2015	Observation vs. surgery	145, 76	76 patients had pathologically confirmed PNETs. Eleven (14.5%) and 3 (3.9%) of these 76 patients were diagnosed with NET G2 and G3, respectively. Leisons 1.5 cm or more in size had a higher probability of being classified as NET G2 or G3 compared with PNETs measuring <1.5 cm. Factors associated with NET G2 or G3: (i) Age ≥55 years, tumor size ≥1.5 cm, or tumor growth of ≥20% or ≥5 mm.
Rosenberg [19] et al.	2016	Observation vs. surgery	35, 20	**Non operative:** 15 patients, 10 patients had tumors <2 cm, 5 patients had tumors ≥2 cm. **Operative:** 20 patients, 8 patients had tumors<2 cm, 12 patients had tumors≥2 cm. Median f/u 27.8 months. In both groups, tumors <2 cm had no evidence of progression or metastasis. Operative morbidity 35% related to pancreatic pseudocyst.
Sadot [9] et al.	2016	Observation vs. surgery, matched case-control study	104 observed, 77 matched	**Non-operative**: 104 patients, median follow up 30 months (7–135), 26/104 (25%) underwent subsequent tumor resection, median tumor size at last follow up had not changed (1.2 cm), no metastatses. **Operative:** 77 patients, 72 patients were low grade (G1), 5 patients developed a recurrence after 5.1 years. No disease specific mortality in either groups.
Sallinen et al.	2017	Surgical cohort, 16 institutions	210	Of 210, 138 patients were asymptomatic Median tumor size: 15 mm Parenchyma sparing operation: 42% Postoperative mortality: 0.5%, morbidity was 14.3%, 14/132 patients with lymph nodes retrived had metastatic lymph nodes. Tumor size, biliary or pancreatic ductal dilatation and WHO grade 2–3 were associated with recurrence. In patients with tumors ≤10 mm, disease free at last follow up. 1-3-5- year disease free survival rates for tumors 11–20 mm on preoperative imaging was 95.1%, 91% and 87.3%.

patients with MEN1. Reason for secondary surgery was tumor growth in half of patients undergoing surgery.

Criteria for determining the patients for whom observation is safest have not been well explored. Identifying the patients for whom a non-operative strategy may be trialed requires detecting PNETs with high sensitivity, appropriately staging tumors using available radiologic modalities, and correctly identifying other tumor features that should preclude non-operative management. Although CT is widely used for diagnosis, a retrospective review performed by Fujimori et al. [14] demonstrated that EUS, when compared to CT, MRI, and ultrasound, has the highest sensitivity for PNET detection. Similarly, Anderson and colleagues [27] published the largest single institution study, including EUS evaluation of 82 patients who had clinical or biochemical evidence of neuroendocrine tumors. They found an overall sensitivity and accuracy of 93% when using EUS, thereby supporting the use of EUS as a primary diagnostic modality in these tumors, when available. However, CT still plays an important role in tumor staging, including assessment for distant metastases. In addition to morphologic imaging, nuclear medicine studies are necessary when diagnosing and staging PNET. These modalities take advantage of the fact that many NETs express somatostatin receptors. Currently, somatostatin receptor imaging with radiolabelled somatostatin analogues is widely used for this purpose; however, 68-Gallium-DOTA PET or PET-CT may have diagnostic advantages [29]. When assessing tumor characteristics, there exists heterogeneity in the literature regarding the utility of fine needle aspiration (FNA). Some investigators have relied heavily on pathologic results of FNA biopsies to determine management strategies [24–26, 28]. Fujimori et al. [14] have shown that EUS-FNA can successfully determine tumor grade for lesions <2 cm, though concordance with grading from surgical specimens if poorer for lesions ≥2 cm. Although this may suggest a role for FNA for all small PNETs, the risk and cost of biopsy must also be considered.

At our institution, the decision to surgically resect these tumors is guided by a combination of size, symptoms and higher risk radiologic characteristics including pancreatic duct dilatation, lymph node involvement, significant interval growth, and invasion of adjacent structures or vascular invasion. Patients with non-functional, sporadic tumors <2 cm, with benign radiographic appearance (lack of calcifications, necrosis, local invasiveness or lymph node enlargement) are candidates for observation and can be followed up with appropriately timed surveillance imaging (e.g. every 6-months). Occasionally, larger tumors (>2 cm) are observed due to patient preference, comorbidity and surgical risk.

Our study provides a comprehensive assessment of the tumour

growth patterns of a relatively large cohort of patients with small, non-functional PNETs. Our use of chart review allowed for strict inclusion criteria and accurate information on surgical decision-making. Our study does, however, have limitations. Measurements of tumour growth were limited by the use of different imaging modalities amongst the same patients and inter-observer variation in measurement of these lesions. The measurement error associated with radiologic tumour measurement is demonstrated in the discrepancy between radiologic and pathologic tumour size among resected patients. The differing sensitivities for size between imaging modalities would explain the discrepancy between radiologic and pathologic tumor size. However, this reflects real-world practice where patients may alternate between imaging modalities during the follow-up period. Our study is also limited by relatively short duration of follow up. Given that our centre is a tertiary referral centre many patients opt for follow up locally, limiting our ability to follow them long-term. However, if these patients required surgery due to tumour growth in the follow-up period, they would most likely be referred back to our centre and would have been captured by our study. Our study, therefore, is likely to have captured all patients who underwent surgery during the study period.

In conclusion, radiologic surveillance of patients diagnosed with small ($\leq$2 cm) non-functional PNETs is oncologically safe and does not appear to increase the risk of disease progression to unresectable or metastatic states. Further studies exploring factors associated with erratic or rapid tumour growth are needed to better identify patients for whom early resection is warranted.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Author contributions

Yohanathan – Study concept and design, Analysis and interpretation of data, drafting of manuscript, final approval.

Dossa – Analysis and interpretation of data, drafting of manuscript, final approval.

St. Germain – Study concept and design, drafting of manuscript, final approval.

Golbafian –analysis and interpretation of data, drafting of manuscript, final approval.

Gallinger – Study design and Concept, drafting of manuscript, final approval.

Moulton – Study design and concept, Critical revisions, final approval.

McGilvray – Study design and concept, Critical revisions, final approval.

Greig – Study design and concept, Critical revisions, final approval.

Serra – Study design and concept, drafting of article, final approval.

Wei – Study design and concept, Critical revisions, final approval.

Jhaveri – Study design and concept, Critical revisions, final approval.

Cleary – Study concept and design, Analysis and interpretation of data, Critical revisions, final approval.

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