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Is Surgery Beneficial for MEN1 Patients with Small (≤2 cm), Nonfunctioning Pancreaticoduodenal Endocrine Tumor? An Analysis of 65 Patients from the GTE

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Abstract

Background: The management of small, nonfunctioning pancreaticoduodenal endocrine tumors (NFPET) in multiple endocrine neoplasia type 1 (MEN1) patients is still controversial. We therefore investigated the effect of surgery on survival and tumor progression in MEN1 patients with NFPET ≤2 cm by analyzing data from the Groupe des Tumeurs Endocrines (GTE) registry.

Materials and Methods: Among 579 MEN1 patients in the registry, 65 had NFPET ≤ 2 cm. Fifteen (23%) underwent pancreatectomy, 9 at least segmental pancreatectomies and 6 biopsies or enucleations (the surgery group), and 50 (77%) were followed conservatively (the no surgery group). Age at MEN1 and NFPET diagnosis was similar in both groups, as was size of the primary tumor. Seven (10.8%) patients had metastases. Five metastases were synchronous, and 2 (one in each group) were metachronous. Tumor size was similar in patients with or without metastasis.

Results: There was no perioperative mortality. The average follow-up time after NFPET diagnosis was 6.7 years in the surgery group and 3.3 years in the no surgery group. Three (4.6%) patients died during follow-up, 2 due to NFPET and 1 due to thymus tumor. The 2 patients who died of NFPET had undergone pancreatic surgery at the time of NFPET diagnosis. The 2 groups did not differ significantly with respect to tumor progression [5/15 (33%) vs 6/38 (16%), $P = 0.16$]. Overall

This research was done for the French Endocrine Tumor Study Group.

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life expectancy of patients with NFPET ≤2 cm was not different than that of the 229 MEN1 patients in the registry without any pancreaticoduodenal tumor ($P = 0.33$).
Conclusions: This study suggests that surgery may not be beneficial for MEN1 patients with NFPET ≤2 cm.

The prevalence of nonfunctioning pancreaticoduodenal endocrine tumors (NFPET) in patients with multiple endocrine neoplasia type 1 (MEN1) is steadily increasing as a result of earlier diagnosis after genetic testing, better standardized follow-up care, and more sensitive imaging studies for detecting pancreatic tumors. NFPET are currently the most frequent pancreaticoduodenal tumors in MEN1 patients.[1–4] In a recent study that used prospective endoscopic ultrasonography in patients diagnosed with MEN1, 55% had NFPET at an average age of 39.[5]

Nonfunctioning NFPET are a significant cause of death in MEN1 patients,[4,6–9] and the consensus is that patients with tumors greater than 2 or 3 cm should undergo resection.[2,10,11] However, pancreatic surgery is associated with significant mortality and morbidity,[2,12–15] and there is still controversy about the risk–benefit ratio of surgery in patients with small (≤2 cm) NFPET.

We have previously shown that 27% of MEN1 patients with NFPET between 2.1 and 3.0 cm had synchronous or metachronous metastasis whereas 11% with tumor size ≤2 cm had metastasis.[4] We thought an approximately 10% risk of having or developing metastasis could be considered clinically acceptable since the mortality rate for pancreatic resection ranges from 3.8% to 17.6%[13] and the rate of long-term postoperative diabetes was 81% in MEN1 patients who underwent aggressive surgery for pancreaticoduodenal tumors.[12] We therefore chose a threshold of 2 cm in order to investigate the effect of surgery on survival and tumor progression in MEN1 patients with small NFPET.

PATIENTS AND METHODS

The Groupe des Tumeurs Endocrines (GTE; endocrine tumor study group) was created in 2002 by the fusion of the Groupe d'Etude des NEM1 (GENEM; study group on MEN1) and the Groupe d'Etude des Tumeurs à Calcitonine et NEM2 (GETC; study group on calcitonin-producing tumors and MEN2). One of the tasks of the GTE is to maintain a registry of patients with MEN1. The registry, which is maintained at the Center for Epidemiology of the Population at the University of Bourgogne in Dijon, France, is sent reports on MEN1 patients from the 2 French laboratories accredited for genetic testing of MEN1 and patients' physicians. Registry data for MEN1 patients includes results of genetic testing, clinic visit reports, operative reports, pathology reports, and hospital discharge summaries.

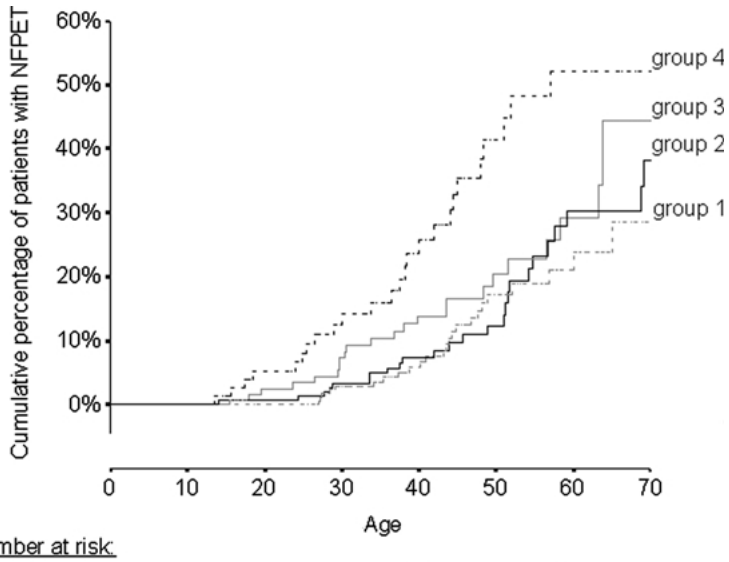
As has been previously described,[4] patients with NFPET were identified among MEN1 patients included in the GTE registry who were diagnosed from June 1956 to April 2003. Briefly, NFPET was diagnosed when one or more pancreatic solid nodules were evidenced by any imaging studies and after excluding gastrinomas, insulinomas, glucagonomas, VIPomas or somatostatinomas.[16,17] A total of 65 patients with NFPET≤2 cm were identified in the registry. Patients were separated into a surgery group, which consisted of those who underwent pancreatectomy, and a no surgery group, which consisted of patients who were followed conservatively (*e.g.,* watchful waiting). Penetrance of NFPET in the MEN1 population of the registry was estimated using the Kaplan–Meier method for 4 different time periods, according to MEN1 diagnosis date. The dates for separating the 4 groups were chosen in order to have 4 quartiles consisting of similar numbers of patients with NFPET: groups 1, 2, 3, and 4 were defined as MEN1 diagnosis before 1989, between 1989 and 1994, between 1995 and 1998, and after 1998, respectively.

Results are presented as mean values ± standard deviation (SD) unless otherwise stated. Comparisons between groups were made using the chi-square test, Fisher's exact test, or Student's *t*-test. Survival data were analyzed using the Kaplan–Meier method, and groups were compared using the log-rank test. P values <0.05 were considered statistically significant. Statistical analyses and graphs were performed with SPSS software version 11.0.1 (SPSS Inc., Chicago, IL, USA). Legends and numbers of patients at risk were added on the graphs using Adobe Photoshop Elements (Adobe Systems Incorporated, San Jose, CA, USA).

RESULTS

Increasing Frequency of NFPET in MEN1 Patients Over Time

Over the 4 time periods, the percentage of patients with NFPET increased steadily from 13.2% in group 1 to



Number at risk:

Group 1	188	182	116	29
Group 2	166	160	100	29
Group 3	126	113	69	18
Group 4	83	68	36	11

Figure 1. Cumulative percentage of nonfunctioning pancreaticoduodenal endocrine tumors (NFPET) by age in multiple endocrine neoplasia type 1 (MEN1) patients. Patients were separated into 4 groups according to the date of MEN1 diagnosis: group 1 (<1989), group 2 (1989–1994), group 3 (1995–1998), group 4 (>1998). The number of patients at risk at each age is shown below the graph.

16.0% in group 2, 19.5% in group 3, and 31.4% in group 4. The estimated penetrance of NFPET in MEN1 patients by age 40 increased over time and was 5.9% (95% CI: 2.1–9.6) in group 1, 7.5% (95% CI: 3.0–11.9) in group 2, 13.9% (95% CI: 7.0–20.7) in group 3, and 23.7% (95% CI: 12.9–34.4) in group 4 (Fig. 1). Moreover, over time, NFPET was being diagnosed at a younger age, as shown by the shift of the curves to the left side of the axis in Fig. 1.

Patient Characteristics and Follow-Up

Of the 108 patients with isolated NFPET in the registry, 65 had tumors ≤2 cm. When we divided those patients into 2 groups (surgery vs no surgery), they did not differ significantly with respect to age, delay between MEN1 and NFPET diagnosis, and tumor size (Tables 1 and 2). NFPET was diagnosed by imaging studies in 51 patients (79%), by pancreatic polypeptide increase in 4 patients, and by unknown means in 10 patients. Nearly 80% of patients had multiple tumors. Patients in the surgery group had more NFPET and more metastases (Table 2); however, this may be due to the longer follow-up period for that group (Table 3). Tumor size was similar in both groups (Table 2) and in patients with or without metastasis (1.30 ± 0.35 cm vs 1.22 ± 0.44 cm, $P = 0.63$). The two patients who developed metachronous metastases had primary tumors of 1.2 and 2.0 cm.

Fifteen patients underwent surgery for their NFPET. Six underwent limited resection (biopsy or enucleation only), and nine underwent at least a segmental pancreatectomy (Table 4). There were no perioperative deaths. Average follow-up time after NFPET diagnosis was 6.7 years in the surgery group and 3.3 years in the no surgery group. Three patients died during follow-up: 2 following NFPET metastasis at age 39 and 57 several years after having undergone surgery at the time of NFPET diagnosis (Table 4) and the third of a thymus tumor at age 44. Although more patients in the surgery group had disease progression or died than in the no surgery group, the differences were not statistically significant (Table 3). Finally, overall life expectancy was similar for patients with NFPET ≤2 cm and the 229 MEN1 registry patients who did not have NFPET (Fig. 2). In this latter group, 8 died of MEN1-associated lesions and 8 of diseases unrelated to MEN1.

DISCUSSION

In this retrospective, registry-based study, we confirmed that the prevalence of NFPET among MEN1 patients increased over time. Moreover, we found that MEN1 patients with small NFPET ≤2 cm did not have shorter life expectancy than those who did not have any

Table 1.
Characteristics of the 65 multiple endocrine neoplasia type 1 (MEN1) patients with nonfunctioning pancreaticoduodenal endocrine tumors (NFPET) ≤2 cm

	No surgery group (n = 50)	Surgery group (n = 15)	*P* value
Age at MEN1 diagnosis	35.6 ± 13.0	36.0 ± 15.4	0.97*
Time between MEN1 diagnosis and NFPET diagnosis	6.1 ± 5.4	6.7 ± 9.1	0.78*
NFPET leading to diagnosis of MEN1	2 (4%)	1 (7%)	0.67**
Median date of NFPET diagnosis	June 1999	January 1995	
Associated MEN1 lesions			
NFPET + para	15 (30%)	10 (67%)	
NFPET + para + pit	15 (30%)	1 (7%)	
NFPET + para + pit + adre	8 (16%)	7 (1%)	
NFPET + para + adre	6 (12%)	2 (13%)	
NFPET alone	2 (4%)	0	
NFPET + pit	2 (4%)	0	
NFPET + para + carc	1 (2%)	0	
NFPET + para + carc + adre	1 (2%)	0	
NFPET + carc	0	1 (7%)	

Para: parathyroid; pit: pituitary; adre: adrenal; carc: carcinoid.
Results are mean ± SD or values (percent).
*Student's *t*-test.
**Chi-square test

Table 2.
Nonfunctioning pancreaticoduodenal endocrine tumor (NFPET) characteristics

	No surgery group (n = 50)	Surgery group (n = 15)	*P* value
Number of tumors	2.7 ± 2.1	4.8 ± 2.2	0.048*
Size of the biggest tumor	1.17 ± 0.42	1.41 ± 0.40	0.059*
Location			0.72**
Head	8 (16%)	4 (27%)	
Body	7 (14%)	1 (7%)	
Tail	7 (14%)	4 (27%)	
Head + body + tail	6 (12%)	3 (20%)	
Head + body	5 (10%)	0	
Body + tail	4 (8%)	2 (13%)	
Head + tail	2 (4%)	1 (7%)	
N/A	11 (22%)	0	
Presence of metastasis	3 (6%)	4 (27%)	0.044***
Lymph nodes	0	3 (20%)	
Liver	3 (6%)	2 (13%)	
Synchronous	2 (4%)	3 (20%)	
Metachronous	1 (2%)	1 (7%)	

N/A: information not available; presence of metastasis: denotes the number of patients with single or multiple metastases.
Results are mean ± SD or values (percent).
*Student's *t*-test.
**Chi-Square test.
***Fisher's exact test.

pancreaticoduodenal tumors. We also found that the proportion of patients with NFPET who had tumor progression or died did not differ significantly between those who underwent surgery and those whose tumors were managed conservatively.

Historically, lack of a clinical syndrome associated with NFPET in MEN1 patients resulted in these tumors being discovered very late, often when patients had a palpable abdominal mass and lymph node and distant metastases. However, thanks to better knowledge of MEN1

Table 3.
Follow-up of patients with nonfunctioning pancreaticoduodenal endocrine tumor (NFPET) ≤2 cm

	No surgery group (n = 50)	Surgery group (n = 15)	*P* value
Follow-up time (years)	3.3 ± 2.6	6.7 ± 4.0	0.001*
Progression/recurrence of tumor [n/n at risk (percent)]	6/38 (16%)	5/15 (33%)	0.156**
Reoperation	0	1 (7%)	
Deaths [n/n at risk (percent)]	1/38 (3%)	2/15 (13%)	0.190***
Related to NFPET	0	2 (13%)	
Unrelated to NFPET	1 (3%)	0	

Progression/recurrence of tumor and deaths: in the no surgery group, 12 patients were diagnosed with NFPET after January 1999 and had no follow-up data available in the registry; therefore 38 patients were at risk in this group.

Results are mean ± SD or values (percent).

*Student's *t*-test.

**Chi-Square test.

***Fisher's exact test.

disease and to genetic testing available since 1997, many patients in a familial setting of MEN1 are now diagnosed on a genetic basis only and are then treated using well-established protocols.[11,18,19] These treatment protocols always include pancreatic imaging studies, which have become more sensitive during the last decade. Endoscopic ultrasonography is currently the most sensitive imaging study available for detecting pancreatic lesions[20–22] and can detect lesions as small as 2 mm.[5] Systematic use of sensitive pancreatic imaging studies in patients diagnosed with MEN1 at a younger age led to an increased recognition of NFPET so that they have now become the most frequent pancreaticoduodenal lesions in patients with MEN1.[1–3] Using the GTE registry data, we confirmed that the frequency of NFPET progressively increased over the 4 time periods studied, with the biggest increase taking place since 1998. Moreover, previous autopsy data showing that more than 80% of MEN1 patients have some pancreaticoduodenal tumors[23] are now confirmed by clinical studies, including 2 from the GTE showing that 55% of MEN1 patients have pancreaticoduodenal tumors at a mean age of 39 when endoscopic ultrasonography is used prospectively[5] and that the estimated cumulative frequency of pancreaticoduodenal tumor is 84% at age 80.[4] Because NFPET represents a significant cause of death in MEN1 patients, several groups have proposed an aggressive approach to these tumors, recommending excision of every tumor evidenced by imaging studies or biochemically proven.[1,3,8,12] However, this high frequency of NFPET leads to a new clinical problem: whether all patients with MEN1 should undergo pancreatectomy with the aim of preventing cancer. This is controversial first because NFPET are a significant cause of death in MEN1 patients, accounting for 39% of the MEN1-related mortality but only for 15% of overall mortality,[9] far below the 55%–84% frequency of pancreaticoduodenal tumors; second, because pancreatic surgery is associated with significant mortality and morbidity (unlike prophylactic thyroidectomy in MEN2); and third, because cancer prevention is not totally achieved with less than total pancreatectomy.

In this study, each patient's treatment was decided upon by the physicians in charge of that patient and did not follow specific recommendations. The fact that primary tumor size was similar in the surgery group and the no surgery group and that the median date of NFPET diagnosis in the no surgery group was 4.5 years later than in surgery group suggests that physicians in charge of these MEN1 patients tended to be less aggressive over time in how they treated tumors ≤2 cm. This tendency is further confirmed by the fact that although 35 patients were newly diagnosed with NFPET ≤2 cm since January 1999, only 2 underwent surgery for their tumors. Our finding that patients in the surgery group had more tumors and more metastases is not surprising because preoperative imaging studies always underestimate the extent of disease, particularly the number of small pancreatic tumors and lymph node metastasis, as other studies have shown.[24] Therefore, we think these differences in the two groups represent the difference in detection modality (pathology report versus imaging studies) and not a true difference.

This study did not show any survival benefit for patients with NFPET ≤2 cm who underwent surgery compared with patients who had conservative management (watchful waiting). Moreover, in the surgery group,

Table 4.
Characteristics and follow-up data for the 15 patients who had surgery for nonfunctioning pancreaticoduodenal endocrine tumor (NFPET)

	Age MEN1 diagnosis	Age NFPET diagnosis	Synchronous metastasis	Type of operation	Tumor size (mm)	Follow-up (years)	Status at follow-up
1	46	46	No	Biopsy	14	6.3	Alive, multiple NFPET
2	32	38	No	Enucleation	15	3.7	Alive, free of tumor
3	13	14	No	Enucleation	15	1.2	Alive, free of tumor
4	27	45	No	Enucleation	20	6.7	Alive, free of tumor
5	62	63	No	Enucleation	8	4.6	Alive, free of tumor
6	14	14	No	Enucleation	20	4.4	Alive, free of tumor
7	30	30	LN	Whipple + LN dissection	15	9.6	Recurrence, reoperation then dead of NFPET
8	48	48	No	Left pancreatectomy	15	16.4	Alive, free of tumor
9	41	51	No	Left pancreatectomy	10	5.8	Alive, free of tumor
10	63	64	No	Left pancreatectomy	20	1	Alive, multiple liver metastasis 1 year after operation
11	34	52	No	Left pancreatectomy	10	5.1	Alive, free of tumor
12	24	24	No	Left pancreatectomy + cephalic enucleation	17	9.8	Alive, free of tumor
13	49	49	No	Left pancreatectomy + cephalic enucleation	10	8.7	Alive, free of tumor
14	36	36	LN	Left pancreatectomy + cephalic enucleation + LN dissection	11	9.8	Alive, new NFPET 6 years after operation
15	23	49	Liver + LN	Subtotal pancreatectomy + liver biopsy	11	7.7	Dead of NFPET

MEN1: multiple endocrine neoplasia type 1; LN: lymph node.

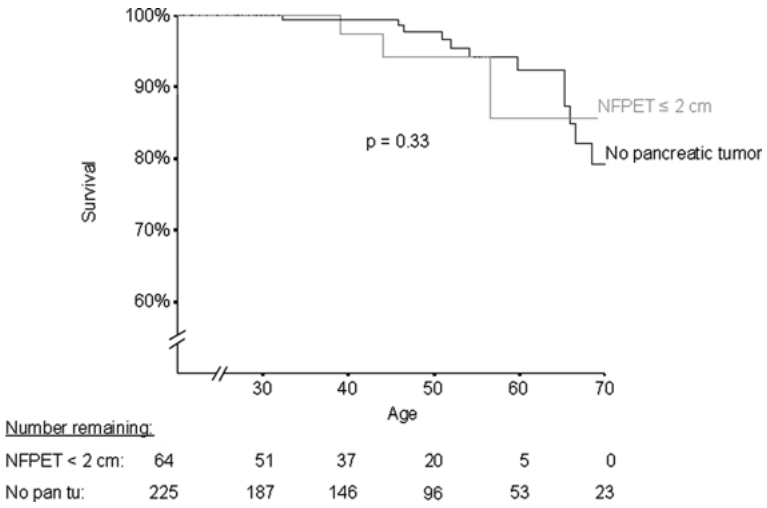


Figure 2. Kaplan–Meier graph comparing life expectancy for multiple endocrine neoplasia type 1 (MEN1) patients with nonfunctioning pancreaticoduodenal endocrine tumor (NFPET) ≤2 cm with that of MEN1 patients without pancreaticoduodenal tumor. The number of patients remaining at each age is shown below the graph.

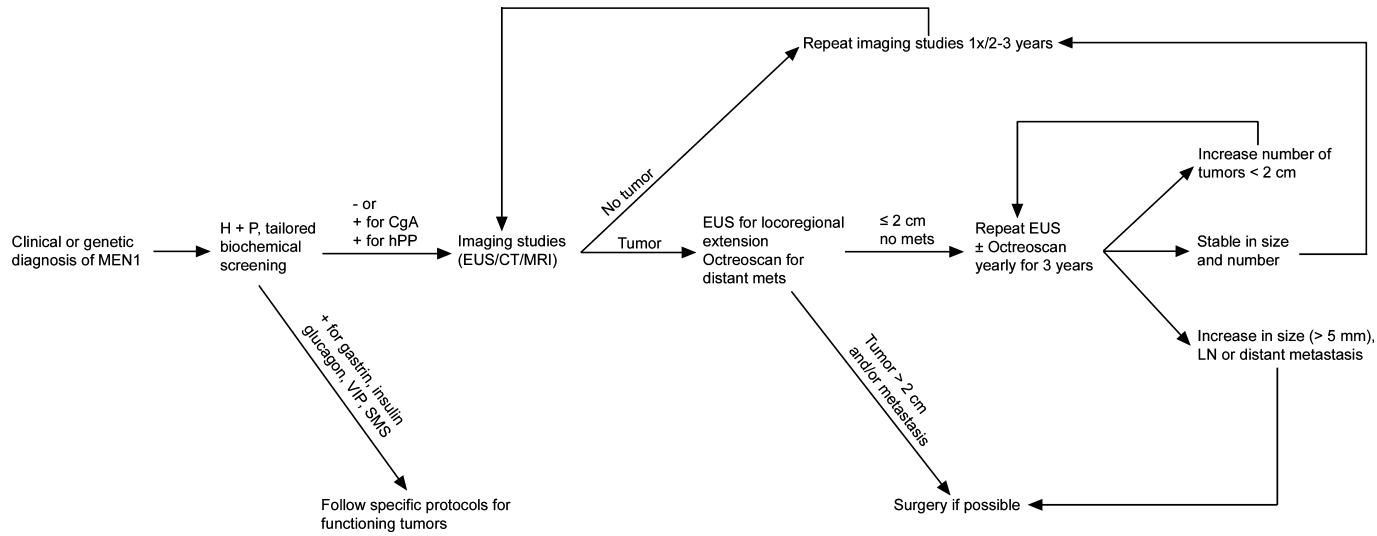


Figure 3. Proposed algorithm for detection and management of nonfunctioning pancreaticoduodenal endocrine tumors (NFPET) in multiple endocrine neoplasia type 1 (MEN1) patients. H+P: history and physical examination; tailored biochemical screening: according to signs and symptoms and following specific protocols; CgA: measurement of blood levels of chromogranin A; hPP: human pancreatic polypeptide gastrin, insulin, glucagons; VIP: vasoactive intestinal peptide; SMS: somatostatin; −: negative; +: positive; EUS: endoscopic ultrasonography; CT: computer tomography; MRI: magnetic resonance imaging; LN: lymph node, mets: metastasis. (1) We do not recommend systematic dosage of hPP for NFPET diagnosis since its increase does not change the management of those patients. (2) Because the risk of developing a new tumor ≥2 cm seems low in patients without any tumor at first pancreatic imaging studies, some authors recommend an EUS every 5 years for the follow-up of those patients.

progression or recurrence of NFPET was as frequent as in the no surgery group, which suggests that surgery did not prevent death or tumor recurrence in these patients. Even though the follow-up period was shorter for patients in the no surgery group, and even though the surgery consisted of biopsy or enucleation only in 6 patients, the numbers of deaths and recurrences observed make it very unlikely that over a longer period, surgery would have an advantage over conservative management. However, because of the retrospective nature of this study, and because we could not always find the reason why a patient was operated on, it is possible that patients in the surgery group were identified as having more aggressive disease and that the 2 groups are, in fact, different in terms of tumor aggressiveness. Nevertheless, this study suggests that patients with small NFPET and

without sign of tumor aggressiveness can safely be followed without rapid growth of a known tumor or development of new tumors or metastases. Because of the short follow-up in this study, long-term studies are warranted to confirm this approach.

This study suggests that NFPET can follow different patterns: many patients present with pancreaticoduodenal tumors, but few develop aggressive disease leading to death. Additional clinical, biologic, or genetic markers of tumor aggressiveness are needed to better predict which patients are at greater risk for death and which will have stable disease for years or decades. In our opinion, the only currently available markers for aggressiveness are primary tumor size, rapid growth of an existing tumor, or the new appearance of a lymph node or distant metastasis. We therefore recommend operating on patients with NFPET >2 cm, patients with NFPET that increase by >5 mm in 1 year, and patients with newly detected lymph node metastasis or distant metastasis (Fig. 3). Endoscopic-ultrasonography-guided fine-needle aspiration is available and can be used to determine whether a suspicious lymph node is benign or malignant.

This study has several limitations. First, the 2 groups are not quite similar because more patients in the surgery group than in the no surgery group were diagnosed during earlier time intervals. However, age at MEN1 diagnosis, delay from MEN1 diagnosis to NFPET diagnosis, and size of the primary tumor were similar in both groups, suggesting that both groups are comparable. Second, the study was retrospective and multi-institutional, and the patients were not randomly assigned to one or the other group and were followed with different protocols according to the timing of diagnosis and the institution. Moreover, the type of operation was not always a left pancreatectomy with cephalic enucleation, which would be the recommended procedure by the Uppsala and Ann Arbor group.[3,12] Because of the small number of patients involved, a subgroup analysis of patients after the Ann Arbor procedure was not performed; however, the information on each individual patient is given in Table 4. Third, the study has a rather short follow-up considering the relative indolent evolution of these tumors.

In conclusion, we believe that the risk–benefit ratio of surgery versus conservative management of small, nongrowing NFPET in MEN1 patients is in favor of conservative management. We therefore recommend that physicians who treat patients with MEN1 follow the algorithm for detection and management of NFPET shown in Fig. 3.

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