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ORIGINAL ARTICLE

Long-term outcomes in patients with multiple endocrine neoplasia type 1 and pancreaticoduodenal neuroendocrine tumours

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Summary

Background In patients with multiple endocrine neoplasia type 1 (MEN-1), pancreaticoduodenal (PD) neuroendocrine tumours (NETs) are associated with early mortality, yet the best treatment strategy remains uncertain.

Aim To assess patient important outcomes (mortality and metastasis) of PD-NETs and predictors of outcomes in patients with MEN-1.

Methods Retrospective cohort of patients with MEN-1 who attended the Mayo Clinic, Rochester, MN from 1997 to 2014.

Results We identified 287 patients with MEN-1; 199 (69%) patients had 217 PD-NETs. Among those with a PD-NETs, 129 (65%) had surgery of which 90 (70%) had their primary surgery performed at Mayo Clinic. The median postoperative follow-up was 8 years during which 13 (14%) patients died. The mean (±standard deviation) age of death was 51 (±9) years. Tumour size, metastasis at surgery or tumour type were not predictive of mortality, but for every year older at surgery, the odds of metastasis increased by 6%. Surgery was not performed in 70 (35%) patients. Among those who were observed/medically managed without known metastatic disease, mean tumour growth was 0·02 cm/year (range, −0·13–0·4 cm/year). Four patients (7%) died at a median age of 77 (range, 51–89) years.

Conclusion PD-NETs are common in patients with MEN-1 and are associated with early mortality even after surgical intervention. Active surveillance is a viable option in nonaggressive PD-NETs, although definitive factors identifying such patients are lacking. Therefore, counselling regarding risks and benefits of current treatment options remains integral to the care of patients with MEN-1.

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Introduction

Multiple endocrine neoplasia type 1 (MEN-1) is a rare autosomal dominant disorder due to a germline mutation of *MENIN* on chromosome 11q13.[1,2] Loss of this tumour suppressor gene may lead to the development of parathyroid, pancreaticoduodenal and pituitary tumours and less commonly bronchial, thymic and adrenal tumours as well as cutaneous lesions.[3,4] While parathyroid tumours, in patients with MEN-1, are the most common manifestation and are associated with morbidity, pancreaticoduodenal (PD) neuroendocrine tumours (NETs) pose the greatest mortality risk.[5–7]

PD-NETs occur in 70–80% of patients with MEN-1 and may be classified as nonfunctional or functional tumours (e.g. gastrinoma, insulinoma, vasoactive intestinal polypeptide [VIP] secreting tumour [VIPoma] or glucagonoma) depending on the presence or absence of a hormonal syndrome.[8,9] Historically, death in patients with MEN-1 was attributed to the consequences of excess gastric acid secretion including gastrointestinal bleeds and ulceration.[10,11] However, with the development of effective medical therapy to reduce gastric acid secretion, metastatic PD-NETs have now become the leading cause of death.[6,12,13]

Although the ideal treatment strategy for PD-NETs is uncertain, it is clear that the overall goal is to control symptoms and disease burden without any detrimental effect on the quality of life.[9] However, there is paucity of data to help clinicians identify the exact time in which the benefits of treatment (surgical or medical) outweigh the possible risks. In fact, researchers have been unable to find a genotype/phenotype correlation and markers of aggressive disease (rapid growth and or malignant potential) remain elusive.[14–17] Moreover, there is conflicting evidence to suggest that metastases are more likely to occur with larger

tumours.[18,19] To address this knowledge gap, we describe the natural history of a large cohort of patients with MEN-1 and PD-NETs managed at a single institution and assessed patient important outcomes such as mortality, predictors of mortality and metastasis among those who were managed with active surveillance or surgically.

Methods

Following approval from the Mayo Foundation Institutional Review Board, we performed a retrospective analysis of patients with a diagnosis of MEN-1 (International Classification of Disease code (ICD-9)-258·01) who had attended the Mayo Clinic, Rochester, MN, from 1997 to 2014. Electronic medical records were assessed for demographic and clinical data regarding PD-NETs including biochemical testing, radiological imaging, surgical procedure, associated surgical complications and pathology results.

Diagnosis of MEN-1

In keeping with current clinical guidelines, the diagnosis of MEN-1 was made in patients who met one of the following criteria: 1. the presence of two or more MEN-1-associated endocrine tumours; 2. the occurrence of a MEN-1-associated tumour in a patient with a family history of MEN-1; and 3. the identification of a germline MEN-1 mutation.[9]

PD-NET diagnosis

A diagnosis of Zollinger–Ellison syndrome (ZES) was based on the presence of typical hypergastrinaemia symptoms (e.g. gastric ulceration) and the presence of an elevated gastrin level. The diagnosis of an insulinoma was based on the confirmation of Whipple's triad followed by biochemical confirmation of endogenous hyperinsulinism.[20] The diagnosis of a VIPoma or a glucagonoma was based on symptoms and VIP levels or a glucagon level ≥2 times the upper limit of normal. A nonfunctioning PD-PNET diagnosis was based on the presence of a pancreatic tumour in the absence of a hormonal syndrome. Metastasis was defined as tumour deposits in lymph nodes or liver seen on radiological imaging and/or on pathology.

Treatment of PD-NET

Treatment modalities (active surveillance or surgery) for PD-NETs were based on the clinical assessment of the treating physician in the context of the values and preference of each patient and in keeping with current and previous guidelines.[9,21] Generally, surgery was recommended when symptoms of hypergastrinaemia failed to respond to medical management (including proton pump inhibitors and/or H2 receptor antagonists at recommended manufacturer doses or higher) or when the largest PD-NET approached 2 cm in diameter. Active surveillance was recommended when the tumour was <1 cm in diameter. For PD-NET between 1 and 2 cm in size, the risks and benefits of surgery *vs* observation were discussed with the patient.

Enucleation was performed if a solitary tumour was identified and was >3 mm from the pancreatic duct. Distal pancreatectomy was the treatment of choice with or without enucleation if there were more than one tumour present in the distal pancreas. In the setting of gastrinomas, duodenotomy with excision of identified tumours was performed or a pancreaticoduodenectomy was performed when head of pancreas lesions were identified. Liver metastases, when present, were either resected or treated with radiofrequency ablation if feasible.

Tumour growth

Among those who did not have surgery and had nonfunctioning PD-NETs, the annual rate of PD-NET growth was calculated. Functioning PD-NETs were not assessed for tumour growth as insulinomas are primarily resected, and a majority of gastrinomas are duodenal making size assessment and source of metastases challenging. Tumour growth was assessed by documenting the rate of change in diameter (cm/year) of the largest tumour in those who had no metastasis at baseline and had the same imaging modality performed at least twice separated by at least a year. If more than one scan was performed on follow-up, the first and the last were used for comparison. Direct comparison of largest tumour size was performed by the reporting radiologist.

Statistical analyses

Categorical variables were summarized as percentages and continuous variables were expressed as a mean and standard deviation when normally distributed; otherwise, median values with interquartile range (IQR) are presented. For survival analysis, the time of first surgery at Mayo Clinic (expressed in years) was considered as time zero and patients were followed until death or last contact. Survival probability was analysed using the Kaplan–Meier method, and comparisons between groups assessed using the log-rank test. Logistic regression was used to assess for predictors of metastasis at surgery including age, sex, tumour size and tumour type in a univariate model. Cox model was used to assess predictors of mortality after surgery including age, sex, tumour size [as a continuous variable and as a binary variable (tumours <2 cm compared to tumours ≥2 cm and tumours <3 cm compared to tumours ≥3 cm)], tumour type and the presence of metastasis at surgery in a univariate model. The category 'other' was excluded from the variable tumour type as there was only one patient with this and was deemed too small for comparison. Differences with a significance level $P < 0{\cdot}05$ were considered to be statistically significant. Statistical analysis was performed using JMP statistical package.

Results

During the study period (1997–2014), 287 patients who attended the Mayo Clinic had a diagnosis of MEN-1. The majority were women ($n = 167$, 58%) with an average age at diagnosis of MEN-1 of 37 (±17) years (Table 1). The most common clinical manifestation of MEN-1 was primary hyperparathyroidism

Table 1. MEN-1 cohort demographics and mortality

Characteristics	Patients (n = 287)
Mean age at diagnosis of MEN-1, years ± SD	37 ± 17
Mean age of diagnosis of PD-NET, years ± SD	42 ± 14
Female	167 (58%)
Other manifestations of MEN-1	
Primary HPT	255 (89%)
Pituitary tumour	139 (48%)
Adrenal mass	37 (13%)
Bronchial/thymic NET	24 (8%)
Died	43 (15%)

HPT, hyperparathyroidism; MEN-1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumour; PD, pancreaticoduodenal.

(n = 255, 89%) followed by PD-NETs (n = 199, 69%). There were 217 PD-NETs identified in 199 individuals, and most of which were nonfunctioning PD-PNETs (110/217, 55%). Among functioning PD-NETs, gastrinomas (n = 73/107, 68%) were the most common followed by insulinomas (30/107, 28%), and VIPomas/glucagonoma (4/107, 4%) (Fig. 1). The average age at diagnosis of a PD-NET was 42 (±14) years. Overall, 43 (15%) individuals with MEN-1 died. The cause of death was known in 26 (60%), 21/26 (81%) were MEN-1 related and 17/21 (65%) of which were due to metastatic PD-NET.

Surgical management of PD-NET

Surgery was performed in 128 (64%) patients of which 90 (70%) had their primary surgery performed at Mayo Clinic (Fig. 2). The surgical procedures performed for treatment of PD-NET among those who had their primary surgery at Mayo Clinic are presented in Table 2. There were no surgery-related deaths. Surgical procedure-related complications occurred in 23 (26%) patients. The most common complication was a pancreatic leak which occurred postoperatively in 12 (13%) patients (Table 3). Diabetes developed postoperatively in nine (10%) patients with six requiring insulin.

Among those who had their first surgery at Mayo Clinic, the median size of the largest tumour was 2·3 cm (range, 0·3–25 cm) and the average age at diagnosis of PD-NET was 39 years (±14) [see Table 2 for information according to tumour subtype]. Metastases were present at surgery in 31% (28/90) of patients (lymph nodes, n = 11; liver, n = 14; both liver and lymph nodes, n = 3). Metastases present at surgery were seen in five of nine patients who had subcentimetre PD-NETs (i.e. tumours <1 cm). There was no association between sex or size of the largest tumour at surgery and the presence of metastasis (Table 4). For each year older a patient was at the time of surgery, the odds of metastasis increased by 6%. The odds of metastasis at surgery differed by tumour type with metastatic disease more likely in gastrinomas compared to nonfunctioning PD-NETs or insulinomas (P = 0·043); however, given that there were only four events, this needs to be interpreted accordingly.

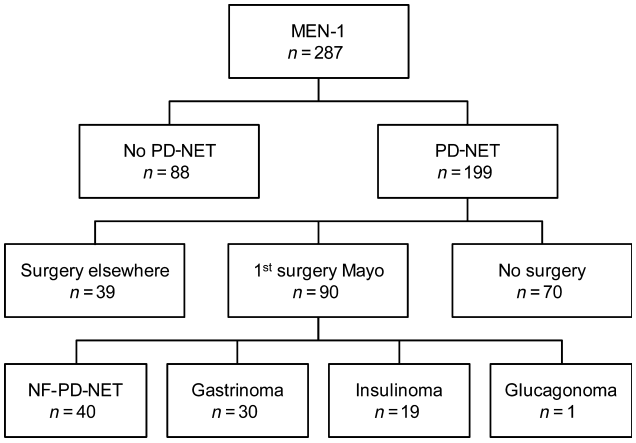

Fig. 1 Patient identification flow diagram. Abbreviations: MEN-1, multiple endocrine neoplasia type 1; n, number of patients; NF, nonfunctioning; NET= neuroendocrine tumour; NF= nonfunctioning; PD= pancreaticoduodenal.

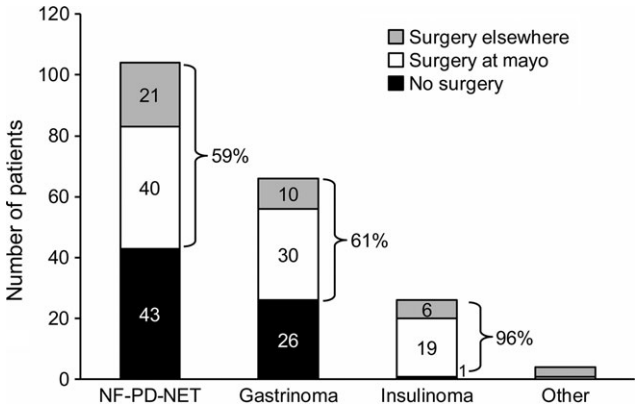

Fig. 2 Treatment received according to type of pancreaticoduodenal neuroendocrine tumour. Brackets indicate percentage that had surgery. Abbreviations: NF, nonfunctioning; PD, pancreaticoduodenal; NET, neuroendocrine tumour.

Among those who had no metastasis identified at surgery, the median tumour size was 2·4 cm (1·8–3·3 cm) and 5/62 (8%) developed metastasis with an average time to metastasis development of 14·8 years. Age, sex and tumour size were not associated with the risk of metastasis after surgery; however, given that there were only five events, this needs to be interpreted accordingly.

The median postoperative follow-up for all of those patients who had their first surgery at Mayo Clinic was 8 years (IQR, 3–38 years). During follow-up in those who had surgery at Mayo Clinic, 13 (14%) died (non-functioning PD-NET, six; gastrinoma, three; insulinoma, three; glucagonoma, one). The cause of death was known in nine (70%) with seven (78%) attributable to MEN-1-related causes [six due to metastatic PD-NET (four nonfunctioning tumours, one gastrinoma and one VIPoma) and one metastatic thymic carcinoid]. The mean age of death was 51 (±9) years. The probability of survival after surgery in those with metastases at surgery compared to

Table 2. Patient demographics, tumour characteristics and surgical complications of those who had surgery at Mayo Clinic

	NF-PD-NET (n = 40)	Gastrinoma (n = 30)	Insulinoma (n = 19)	Other (n = 1)	All (n = 90)
Mean age at diagnosis of PD-NET	36 ± 12	45 ± 11	40 ± 15	38	35·7 ± 14
Female	20 (50%)	19 (63%)	20 (50%)	0	48 (53%)
Median size, cm (IQR)	2·5 (1·9–4·15)	2 (1–3)	2·5 (1·7–3·95)	9·5	2·4 (1·45–3·85)
Mets at surgery	8 (20%)	15 (50%)	4 (20%)	1 (100%)	28 (31%)
Died	6 (15%)	3 (10%)	3 (16%)	1 (100%)	13 (14%)
Surgical procedures					
DP	34	8	14	1	57
DP + enucleation/duodenotomy	3*	9	3		15
Enucleation		7	1		8
Whipple's		1			1
PPPD	2†	2			4
Duodenotomy		3			3
Ethanol ablation	1		1		2

DP, distal pancreatectomy; IQR, interquartile range; mets, metastatic disease; NF, nonfunctioning; PD, pancreaticoduodenal; NET, neuroendocrine tumour; PPPD, pylorus preserving pancreatoduodentomy;
*PPPD, DP, enucleation and ethanol ablation in one patient.
†PPPD, enucleation and DP in one patient.

Table 3. Patient important outcomes during long-term follow-up of patients with MEN-1 and PD-NET*

Intervention	Presence of metastasis at surgery	Developed mets after surgery†	Mortality†	MEN-1-related Death (unknown cause of death)	Surgical complications
Surgery (n = 90)	Present (n = 28) (31%)	14 (50%)	6 (21%)	4 (1)‡	*Procedural-related complications:* 23/90 (25%)
	Absent (n = 62) (69%)	5 (8%)	7 (11%)	3 (4)	Pancreatic Leak, n = 12
					Ileus/obstruction, n = 8
					Infection, n = 4
					Ventral hernia, n = 1
					Anastomotic leak, n = 1
					Thalamic haemorrhage, n = 1
					Nonprocedural-related complications:
					Diabetes, 9/90 (10%)

	Presence of mets at baseline evaluation	Developed mets during follow-up†	Mortality†	MEN-1-related Death (unknown cause of death)	Clinical behaviour during follow-up
Active surveillance (n = 70)	Present (n = 22) (31%)	NA	8 (36%)	6 (2)	NA
	Absent (n = 48) (69%)	0 (0%)	4 (8%)	0 (4)	Growth 0·02 cm/year (−0·13–0·4 cm)

mets, metastatic disease; NA, not applicable;
*Groups are not directly comparable due to unmatched prognosis at baseline.
†Median follow-up with metastasis: 8 years; without metastasis: 9 years; active surveillance without metastasis: 7 years.
‡In one patient, death was due to intra-abdominal abscess.

those without metastasis at surgery was not statistically different (HR: 2·2, 95% CI: 0·7–6·6; P = 0·17). In addition, the risk of death was not significantly increased in those who developed metastasis following surgery compared to those who did not or with increasing tumour size or tumours ≥2 cm (Table 3). Studies suggest that the risk of metastasis is increased among those with gastrinomas ≥3 cm[22]; therefore, we assessed mortality risk in those who had surgery for a PD-NET and had a tumour ≥3cm compared to those with tumours <3 cm and found that it was increased (HR: 16·8, 95% CI: 3·26–307·69; P = 0·0001).

Nonsurgical management of PD-NET

Of the 199 patients with a PD-NET, 70 had active surveillance (nonfunctioning PD-NET, 43; gastrinoma, 26; and one

Table 4. Predictors of patient important outcomes in patients with PD-NET and MEN-1 who underwent surgical intervention

Outcome (*n*/total)	Predictor	*P* value	Estimate (CI)	OR (CI)
Metastasis at the time surgery (28/90)	Age (years)	0·023	0·06 (0·02–0·1)	1·06 (1·02–1·1)
	Sex (female)	0·34	0·22 (−0·23–0·68)	1·5 (0·62–3·82)
	Tumour size (cm)	0·88	0·01 (−0·15–0·15)	1·3 (0·2–46)
	Tumour type†	0·0074		NF *vs* gastrinoma
	NF-PD-NET		−0·53 (−1·4 to −0·37)	0·12 (1·6–13·7)
	Gastrinoma		0·99 (0·35–1·67)	Gastrinoma *vs* insulin
	insulinoma		Reference	4·29 (1·22–17·87)
				NF *vs* insulinoma
				0·94 (0·25–3·96)

Outcome (*n*/total)	Predictor	*P* value	Estimate (CI)	HR (CI)
Development of metastasis after surgery (5/62)*	Age (years)	0·19	0·042 (−0·02–0·1)	1·04 (0·98–1·1)
	Sex (female)	0·67	0·19 (−0·71–1·21)	1·48 (0·24–11·29)
	Tumour size (cm)	0·77	0·025 (−0·25–0·15)	1·03 (0·78–1·16)
Mortality (13/90)	Age (years)	0·35	0·02 (−0·02–0·07)	1·02 (0·98–1·07)
	Sex (female)	0·77	−0·1 (−0·66–0·45)	1·21 (0·4 – 3·78)
	Tumour size (cm)	0·098	0·08 (−0·01–0·14)	1·08 (0·98–1·15)
	Tumour >3 cm	0·0001	1·14 (0·59–2·86)	16·8 (3·26–307·69)
	Tumour type†	0·51		NF *vs* gastrinoma
	NF-PD-NET		0·46 (−0·36–1·30)	1·7 (0·44–7·99)
	Gastrinoma		−0·07 (−1·08–0·79)	Gastrinoma *vs* insulinoma
	insulinoma		Reference	0·6 (0·13–2·3)
				NF *vs* insulinoma
				2·34 (0·54–13·4)
	Metastasis at surgery	0·17	0·39 (−0·18–0·94)	2·2 (0·7–6·6)

MEN-1, multiple endocrine neoplasia type 1; *n*, number of patients with reported outcome; NET = neuroendocrine tumour; NF= nonfunctioning; PD= pancreaticoduodenal.
*Total of 62 patients did not have metastasis at surgery.
†Excluding one patient who had a VIPoma as this group was felt to be too small for comparison.

insulinoma). The average age of PD-NET diagnosis was 46 (±15), and 48 (53%) were female. The reasons for nonsurgical management include small/stable (n = 28), inoperable (n = 21) or managed medically (n = 13) tumours; advised to have surgery, but lost to follow-up (n = 4); and those who did not have surgery for other reasons (metastatic breast cancer, n = 1; lost to follow-up, n = 1 up and awaiting adequate weight loss, n = 2). Surgery was not performed in 22 (31%) patients with PD-NET tumour as 21 were deemed inoperable in the setting of metastatic PD-NET and one individual did not have surgery due to metastatic breast cancer. The most common reason for surveillance was the presence of small (<2 cm) stable tumours and, in the case of gastrinomas, effective medical treatment.

Annual tumour growth was calculated in 21 patients who participated in active surveillance and had nonfunctioning PD-NETs. Tumour growth among these patients was assessed using CT abdomen (n = 15), endoscopic ultrasound (n = 5) or MRI abdomen (n = 1). The median tumour growth per year was found to be 0·02 cm with a range of −0·13 to 0·4 cm/year.

Among those without metastatic disease who were observed/medically managed, four (7%) died at a median age of 77 (range, 51–89) years. The cause of death was dementia in one and unknown in three.

Discussion

PD-NETs are common in patients with MEN-1, yet optimal treatment strategies remain uncertain given the lack of clarity between the risks, benefits and timing of surgical intervention. In this retrospective study of a large cohort of patients with MEN-1 (n = 287), we showed that among those in whom the cause of death was known, PD-NETs are the most common cause of MEN-1-related deaths. In addition, in patients who underwent surgical treatment for PD-NET (median tumour size 2·3 cm and with 30% having metastatic disease at baseline), the presence of metastasis at surgery was not predicted by tumour size. In fact, metastatic disease was seen in some patients with primary tumours measuring less than 1 cm. In this group, 14% of the patients died during a median follow-up of 8 years with increased risk of death in those with tumours >3 cm (65% of the known causes, due to MEN-1). Moreover, in patients who did not have surgical intervention (e.g. small tumours and symptomatically controlled gastrinomas) and were followed with active surveillance 8% died during follow-up [median time of follow-up 7 years (range, 2–13·5)] and none developed metastases.

Our study adds to the body of evidence suggesting that the most common cause of MEN-1-related deaths is metastatic PD-

NET resulting in premature death.[5,6,13] We found that 65% of MEN-1 patients in whom the cause of death was known were attributable to metastatic PD-NET. In addition, the mean age of death in those who had surgery was 51 years of age comparable to a cohort of MEN-1 patients treated at the National Institute of Health (NIH) which was 55 years (106 patients with a mean follow-up of 24·5 years)[6] and remains lower than the average US national average of 78·8 years.

Due to this association between PD-NET and mortality, many groups advocate for early detection and treatment to prevent metastasis and decrease mortality.[23–25] Among those with PD-NET who are surgical candidates, considering surgery early may be beneficial as we showed that for every year older, the presence of metastasis increased by 6%. On the other hand, limitations of the available evidence (small sample size, selection bias, short duration of follow-up, heterogeneity in populations and treatment) and concerns regarding the morbidity, economical and emotional burden of early and aggressive treatment strategies add complexity to our treatment decisions. Given that MEN-1 is a genetic condition that predisposes patients to tumour formation, the risk of developing a new PD-NET remains when limited resections are performed leading some to advocate for early aggressive surgery with the goals of reducing recurrence and mortality.[26] This however is at the expense of significant morbidity including exocrine and endocrine pancreatic insufficiency as well as worsening of quality of life.[27] Even though distal pancreatectomy was the most common procedure performed in our study and was not associated with perioperative mortality, 26% of patients who had surgery developed a surgical complication. This complication rate is comparable to other MEN-1-related cohorts with complication rates reported to be as high as 58% and 21% in non-MEN-1 studies.[14,28,29] Diabetes developed in 10% of patients, again this is comparable to other studies with rates reported to be as high as 34%.[30,31] Therefore, the need, timing and extent of these surgical interventions need to be weighed against the potential benefits, the context, and the values and preferences of the patient.

Determinants of aggressive PD-NET such as malignant potential and rapid growth may help stratify patients according to their risk of early mortality. Such markers would allow clinicians to tailor treatment strategies according to risk with early and aggressive surgery for those patients at greatest risk. The parameters examined here were not predictive of such risk. While there remains no genotype–phenotype correlation, mutations in the *JunD* or *CHES1* interacting domain have been associated with a higher risk of death.[14,16] In addition, higher Ki67, CK19 and C-KIT levels in nonhereditary PD-NET have been associated with decreased survival probability, but this association has not been assessed specifically in MEN-1.[32,33] These mutations and markers were not examined in this study.

Tumour size has been associated with metastasis in some studies, and as such, it has been generally accepted that surgery be performed in tumours >2 cm.[18] Given that tumour size and identification of metastasis is best assessed pathologically, we analysed this association in those who had surgery. We found no association between tumour size and metastases at surgery or during follow-up, results that were similar to those of Lopez *et al.* who studied 16 patients with non-functioning PD-NET with a median follow-up of 109 months. The risk of death after surgery, however, was noted to be significantly increased among those with tumours >3 cm ($P = 0{\cdot}0001$). Given that the average rate of tumour growth in our nonsurgical group on active surveillance and in whom comparative imaging was available was 0·02 cm per year (−0·13–0·4 cm), this suggests a more indolent course in some tumours. Therefore, identifying aggressive tumours traits and treating these early surgically may decrease mortality while minimizing morbidity in those who would have had a more indolent course. This also highlights the need for co-ordinated care in a multidisciplinary centre to provide appropriate follow-up and surgical intervention when needed.

There are several strengths and limitations to our study. Given the rarity of this condition, prospective studies remain challenging and our study includes a large cohort of MEN-1 patients cared for at a single centre reducing heterogeneity. In addition, the duration of follow-up was long. This was a retrospective study and is therefore subject to selection bias, especially among those who had PD-NETs that were 1–2 cm in size where intervention can be driven by patient preference. Also as a single centre study, the results may not apply to patients seen in other settings. Assessment of the cause of death is limited as the cause of death could only be identified in 60% of those who died. Review of the literature, however, would suggest that our findings are comparable to other series. Imaging studies are not as sensitive as surgical pathology for detecting metastasis, and therefore, among those who did not have surgery, it is likely that the absence of metastasis is overestimated. Nevertheless, the mean age of death in this group was 77 years, and therefore, if metastases were present, they were unlikely to be clinically important.

Finally, it is likely that the real benefit of surgery is masked in the study due to lack of an adequate comparative group and selection bias due to our observational retrospective design. While the mean age of death in those who had surgery does not appear to have improved, there were only 13 deaths in the surgical cohort, six of which were PD-NET related. Therefore, it is difficult to assess the effect surgery has on number of deaths, symptom reduction and quality of life given the systemic nature of the disease.

Conclusion

PD-NETs are associated with increased mortality in patients with MEN-1. A subgroup of patients with MEN-1, however, have PD-NETs that appear to have indolent behaviour; given the high morbidity associated with surgical intervention identification of factors which predict aggressive behaviour (mortality, metastasis) to direct therapy will help personalize future care for patients with MEN-1. In the interim, the data available from this study suggest that patients and clinicians should discuss the potential benefits and harms associated with different treatment

options resulting in a treatment decision best suited to the patients' particular context.

Conflict of interests

The authors declare no conflict of interests.

Financial disclosures

The authors declare no financial disclosures.

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