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ORIGINAL SCIENTIFIC REPORT

One-Year Postoperative Mortality in MEN1 Patients Operated on Gastric and Duodenopancreatic Neuroendocrine Tumors: An AFCE and GTE Cohort Study

Niki Christou[1] · Muriel Mathonnet[1,17] · Sébastien Gaujoux[2] · Guillaume Cadiot[3] · Sophie Deguelte[4] · Jean-Louis Kraimps[5] · Jean-Christophe Lifante[6,7] · Fabrice Menegaux[8] · Eric Mirallié[9] · Fabrice Muscari[10] · Bruno Carnaille[11] · François Pattou[12] · Alain Sauvanet[13] · Pierre Goudet[14,15,16]

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Abstract

Importance In MEN1 patients with gastric and duodenopancreatic neuroendocrine tumors (GPD-NET), surgery aims to control secretions or to prevent metastatic spread, but after GPD-NET resection, postoperative mortality may be related to the surgery itself or to other associated MEN1 lesions with their own uncontrolled secretions or metastatic behavior.

Objective To analyze the causes of death within 1 year following a GPD-NET resection in MEN1 patients.

Design An observational study collecting data from the Groupe d'étude des Tumeurs Endocrines (GTE) database. The analysis considered the time between surgery and death (early deaths [<1 month after surgery] versus delayed deaths [beyond 1 month after surgery]) and the period (before 1990 vs after 1990). Causes of death were classified as related to GDP surgery, related to surgery for other MEN1 lesions or not related to MEN1 causes.

Setting GTE database which includes 1220 MEN1 patients and 441 GPD-NET resections.

Participants Four hundred and forty-one GPD-NET resections.

Main outcome measures The primary end point was postoperative mortality within 1 year after surgery.

Results Twenty-four patients met the inclusion criteria (2%). Median age at death was 50.5 years. Sixteen deaths occurred in the 30-day postoperative period (76%). Among the 8 delayed deaths, 3 occurred as a result of medical complications between 30 and 90 postoperative days. After 1990, mean age at death increased from 48 to 58 years ($p = 0.09$), deaths related to uncontrolled acid secretion disappeared ($p < 0.001$) and deaths related to associated MEN1 lesions increased from 8 to 54% ($p = 0.16$).

Conclusion Surgery and uncontrolled secretions remain the two main causes of death in MEN1 patients operated for a GPD-NET tumor. Improving the prognosis of these patients requires a strict evaluation of the secretory syndrome and MEN1 aggressiveness before GDP surgery.

✉ Muriel Mathonnet
mathonnet@unilim.fr

[1] Department of General, Digestive and Endocrine Surgery, Dupuytren University Hospital, Limoges, France

[2] Department of Pancreatic and Endocrine Surgery, Cochin University Hospital, APHP, Paris, France

[3] Department of Hepato-Gastroenterology and Digestive Oncology, Robert-Debré Hospital, Reims-Champagne-Ardennes University, Reims, France

[4] Department of General and Digestive Surgery, Robert-Debré Hospital, Reims-Champagne-Ardennes University, Reims, France

[5] Department of Digestive Surgery, Jean-Bernard University Hospital, Poitiers, France

[6] Department of General, Digestive and Endocrine Surgery, University Hospital of Lyon Sud, Pierre-Bénite, France

[7] EA 7425 HESPER, Health Services and Performance Research, University Claude Bernard Lyon 1, Lyon, France

Abbreviations

AFCE Association Francophone de Chirurgie Endocrinienne

GTE Groupe d'Etude des Tumeurs Endocrines

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant inherited disease that predisposes carriers to various neuroendocrine tumors (NETs). The first criteria for diagnosis were established during the Seventh International Workshop on MEN held in 1999 in Gubbio, Italy [1], and then regularly updated [1–3]. The disorder is related to mutations in MEN1, a gene of approximately 10 kb that encodes for menin, and is located on chromosome 11q13 [4–6]. Gastric and duodenopancreatic NETs (GPD-NETs) are the second most frequent MEN1-associated lesion after hyperparathyroidism and are responsible for the majority of MEN1 cancer-related deaths [7–9]. The three main associated secretions are gastrin, which causes Zollinger–Ellison syndrome (ZES), insulin and glucagon. Surgery in patients with MEN1-related GPD-NETs aims to control insulin and occasionally glucagon or VIP secretion, or to prevent metastatic spread in case of large, non-functional GPD-NETs. Postoperative mortality after duodenopancreatic resection has been thoroughly studied and is as high as 5.7% and 8.1% at 30 days and 90 days, respectively, as reported in a recent multicentric study [10]. These results indicate that postoperative mortality for GPD-NET surgery must be evaluated over a period of time of several months. Additionally, specific types of postoperative death may occur in MEN1 patients. These deaths may be related to other associated MEN1 lesions which interfere with the operative course either because of their secretions or because of their metastatic behavior [8, 9]. Therefore, the aim of this study was to analyze the overall postoperative causes of mortality in MEN1 patients with GPD-NETs within 1 year after surgery using the MEN1 GTE cohort (Groupe d'étude des Tumeurs Endocrines), which is considered representative of MEN1 disease and which is regularly used to assess care practices.

Methods

MEN1 patients

The study population was composed of symptomatic (which corresponds to a hyperparathyroidism or a Zollinger syndrome) MEN1 patients registered in the Groupe d'étude des Tumeurs Endocrines (GTE) database. The purpose of this network, created in February 1991, is to maintain a registry of MEN1 patients at the Center for Epidemiology at the University of Burgundy in Dijon, France, which receives reports from primary care physicians and from five accredited French and Belgian genetics departments that perform genetic testing for MEN1. Registry data include results of genetic testing, clinic visit reports, operative reports, pathology reports, and hospital discharge summaries [8]. The MEN-1 cohort was approved by the Consultative Committee on Treatment of Information in Health Research (file number 12.364) and the CNIL (National Committee for Data Protection, authorization number DR2013-348). Informed consent was not required, but patients and their family were informed about their right to withdraw their data from the cohort. Data collected were incorporated into the GTE database in 1991. MEN1 patients who underwent surgery on their pancreas, duodenum or stomach from June 1956 to November 2017 and who died during the first postoperative year were included in the study.

Indication for surgery must have been directly or indirectly due to MEN1-related NETs of the duodenum, the pancreas or the stomach. Patients who died after liver surgery to remove associated metastases were not included. Criteria for the diagnosis of endogenous hyperinsulinism

[8] Department of General and Endocrine Surgery, Pitié-Salpétrière University Hospital, APHP, Sorbonne University, Paris, France

[9] Department of Digestive and Endocrine Surgery, Hôtel-Dieu Hospital, CIC-IMAD, Nantes, France

[10] Department of Digestive Surgery, Toulouse University Hospital, Toulouse, France

[11] Department of General and Endocrine Surgery, Lille University Hospital, University of Lille, Lille, France

[12] Department of General and Endocrine Surgery, Lille University Hospital, INSERM U1190, University of Lille, Lille, France

[13] Department of Hepato-Pancreato-Biliary Surgery, Paris Diderot University, Beaujon Hospital, APHP, Clichy, France

[14] Department of Digestive and Endocrine Surgery, Dijon University Hospital, Dijon, France

[15] CIC1432, Clinical Epidemiology Unit, INSERM, Dijon, France

[16] Clinical Epidemiology/Clinical Trials Unit, Clinical Investigation Centre, Dijon-Bourgogne University Hospital, Dijon, France

[17] Chirurgie Digestive, Générale et Endocrinienne, CHU de Limoges - Hôpital Dupuytren, 87042 Limoges Cedex, France

were based on the presence of hypoglycemic symptoms associated with low-plasma glucose concentrations in non-diabetic patients (≤ 0.50 g/L), inappropriately high serum insulin (≥ 3 mUI/L) or C-peptide (≥ 0.6 ng/mL), or proinsulin of at least 5.0 pmol/L. The diagnosis of Zollinger–Ellison syndrome was made using the following existing criteria: At least 2 out of 4 National Institute of Health (NIH) criteria at the time of diagnosis [11]: the presence of elevated fasting gastrin (100 pg/mL until 1994 or >200 pg/mL after 1994); presence of an elevated basal acid output (BAO >15 mEq in unoperated patients and < 5 mEq if previous acid-reducing surgery had been performed); positive provocative testing with secretion (a gastrin increase of >200 pg/mL post-injection) or with calcium (an increase >395 pg/mL); histologic confirmation of gastrinoma (i.e., positive immunostaining for chromogranine A, synaptophysin and exclusively for gastrin). Nevertheless, there is an increasing lack of assessment of gastric acidity because of the difficulty in stopping proton pump inhibitors (PPIs). PPIs must be stopped in order to perform the aforementioned tests. Moreover, recent studies show that more than 50% of gastrin assays are not accurate. Therefore, the following criteria, when taken together, have been increasingly used in MEN1 patients [12]: presence of active peptic ulcer disease with prominent gastric folds; improved diarrhea symptoms with PPI; histologic confirmation of gastrinoma (i.e., positive immunostaining for chromogranine A, for synaptophysin and exclusively for gastrin). Precise causes of death were analyzed. The analysis took into account the time between surgery and death (<30 days after surgery [early postoperative mortality] and during the following months during the first year after surgery [delayed postoperative mortality]), the period of time (before 1990 vs after 1990). Causes of death were classified as follows: (1) related to pancreatic, duodenal and gastric surgery [(a) technical causes, (b) associated medical causes (c) metastatic causes], (2) related surgeries on other MEN1 lesions, (3) not related to MEN1. Patients for whom the time between pancreatic resection and death was more than 1 year were excluded.

Statistical analysis

Quantitative data were reported as median. Qualitative data were reported as number of patients (percentage of patients). Comparisons between groups were made using Fisher exact tests for categorical variables and using non-parametric tests for continuous variables. *P* values <0.05 were considered statistically significant. Statistical analyses were performed with Stata software (*Stata 12.0* (*Stata Corp, College Station, TX*)).

Results

There were 1220 patients in the GTE cohort at the time of the study (November 2017). Among these patients, 441 of them had a GPD-NET resection and 49 were operated more than one time which corresponded to 493 GPD-NET surgery. Twenty-two percent of GPD-NET resections were performed before 1990 ($N = 112$) (Fig. 1).

Twenty-four patients fulfilled the mortality inclusion criteria (2.0%). There were 19 men (79%) and 5 women (21%). Median age at death was 50.5 years (mini: 30–maxi: 77). Clinical data for patients who died during the first postoperative year are displayed in Table 1. ZES was found in 20 patients (83%), a pancreatic NET was visible in 17 patients (71%), an insulinoma in 4 (17%), and ECLoma in one (4%). Twenty-two patients had been diagnosed with hyperparathyroidism (92%), 5 with pituitary adenoma (21%) and 9 with adrenal NET (37%).

The death rate decreased during the first period (before 1990) from 26% to reach a minimum in the 1990s at 1.6%. Then, in the second period, the death rate slightly increased from 1.6% in the 1990s to around 5.1% in 2010–2017 (Fig. 2).

Sixteen deaths occurred in the 30-day postoperative period (67%), and 8 additional deaths occurred in the delayed period (33%). Among these 8 delayed deaths, 3 (37.5%) occurred between 30 and 90 postoperative days from medical complications in relation to acid control, Cushing disease and pulmonary embolism (Table 2). Trends in surgical indications and in causes of death according to the period of time (until 1990 vs after 1990) are described in Table 3. Mean age at death increased from 48 to 58 years old ($p = 0.09$). Deaths related to uncontrolled acid secretion disappeared after 1990 ($p < 0.001$), while deaths related to associated MEN1 lesions increased from 8% before 1990 to 45% after 1990 ($p = 0.16$). Indications for duodenopancreatic resection decreased for ZES ($p < 0.01$), whereas they did not change for other tumors.

Causes of deaths are displayed in Table 2. Five deaths (21%) were due to/associated with the impact of MEN1 disease but not related to GPD-NETs. Hyperparathyroidism was involved in 2 deaths: case 24 was a 41-year-old woman operated for a 2-cm non-functional pancreatic NET by enucleation in 2013. Surgery was followed by hypovolemic shock. A bleeding splenic artery was responsible for intra-abdominal hemorrhage which was successfully embolized radiologically. Pyelonephritis developed during a short period of oliguria. The patient died from septicemia and septic shock on postoperative day 10. Pyelonephritis was the direct result of underlying nephrolithiasis associated with non-operated hyperparathyroidism. The pathology report revealed a 2-cm

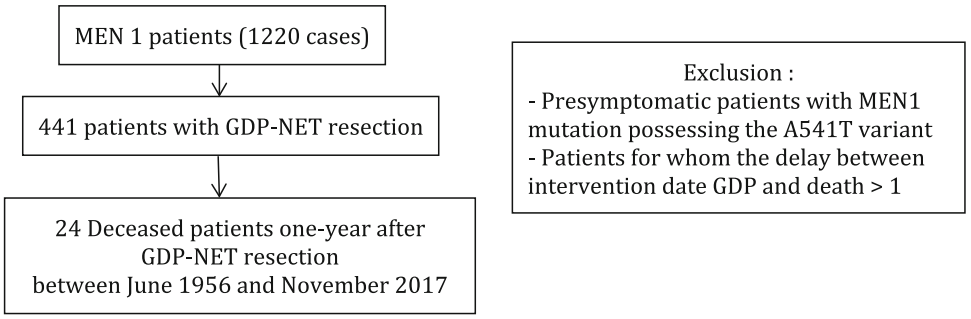

Fig. 1 Diagram of the cohort of MEN1 patients who underwent surgery for gastric and pancreaticoduodenal NETs and died during the first postoperative year

benign NET with a Ki67 <1%. Case 2 was operated on in 1965 for multiple GPD-NETs (3 insulinomas of 3, 1.5 and 1 cm) by total duodenopancreatectomy without confirmation of MEN1 as the underlying disease. Calcemia increased progressively after surgery to reach 3.20 mmol/L. The patient developed anorexia, cachexia, phlebitis and finally died from a pulmonary embolism on postoperative day 250. The diagnosis of MEN1 was established retrospectively. Case 17 was operated for a 2.5 × 2 cm peridoudenal metastatic node. Immunostaining was positive for gastrin. The patient had Cushing syndrome, which was difficult to control with medical treatment. A 6-cm right adrenal tumor was removed during the same surgery. The patient died from metabolic complications due to Cushing syndrome on postoperative day 7. Case 19 had long-standing ACTH-dependant Cushing syndrome and was taking Somatuline, but free urinary cortisol was still elevated. Both adrenal glands were enlarged. The patient had undergone left pancreatectomy for insulinoma several years before followed by the Whipple procedure for a 45-mm cephalic NET. Diabetes due to total pancreatectomy combined with Cushing syndrome was difficult to manage, and the patient died from epilepsy related to hypoglycemia without brain metastases on postoperative day 150. Case 23 was a 75-year-old man with MEN1, who had been diagnosed with a 16-cm tumor developed in contact with the distal pancreas. The resection of the tumor took away the tail of the pancreas and the spleen. The pathological report revealed a 16-cm liposarcoma, and a 15-mm Grade 2 NET was fortuitously discovered in the pancreas. The man died 10 months later from the metastatic spread of the liposarcoma. This death was not GPD-NET related. Three patients (12%) died beyond the first postoperative month from distant GPD-NET metastases. Only one case seemed entirely unrelated to MEN1 disease (work accident).

Discussion

This is the first study to analyze postoperative deaths following resection of duodenal pancreatic or gastric NETs in MEN1 patients whatever the indication for surgery. Indeed, previously published data focused on MEN1 patients operated for non-functioning GPD-NET. They have already shown the risk of postoperative Clavien-Dindo grade III to IV complications of up to 33% [13]. The present study shows that one-third of "operative" deaths within the first year after surgery occurred after the 1-month operating period and affected a higher proportion of men and individuals with Zollinger–Ellison syndrome. Two-thirds of deaths occurred within 90 postoperative days, but none of the deaths was due to the operative procedure between 30 and 90 days. As anticipated, surgery for GPD-NETs and gastric NETs is directly responsible for the majority of operative deaths. Nevertheless, other causes of deaths were encountered which were more frequently due to associated medical conditions or other MEN1 lesions (63%) than to the typical well-known complications of pancreatic surgery (21%).

Several particular aspects of this study should be highlighted: (1) all causes of death occurring during the first postoperative year were analyzed. Analyzing deaths only in the first postoperative month would have underestimated the death rate and would not have sufficiently emphasized the importance of deaths due to aggressive tumors which developed suddenly during the following months and the deaths related to adverse events after pancreatic surgery. Analysis of >30- and 90-day postoperative mortality is the best indicator of procedure quality in pancreatic surgery [14, 15]. Analyzing 1-year postoperative mortality seemed judicious here because MEN1 is a multi-organ disease. (2) This large nationwide GTE cohort of 1220 patients is considered representative of MEN1 disease, of its natural history, of the various treatments and of their complications, and allows to analyze the risk of postoperative mortality and the causes of 441 GPD-NET resections. (3) The study covers a 5-decade period of time, making it

Table 1 Clinical data for patients who died postoperatively in the year following any surgical procedure. $N = 2$

Year of death Cohort number	Sex	Age at death	Previous DP surgery	Underlying DP-NET disease	Indication	Surgery	Mortality (day)	MEN1-related death	Cause of death	pHPT	Pituitary adenoma	Adrenal
1961 No. 1	Male	50	None	ZES +pNET	pNET + ZES	Left pancreatectomy	Operative D8	Yes	Ulcus perforation	Yes	No	Yes
1965 No. 2	Male	38	None	ZES +pNET +Insulinoma	Multiple pNETs + ZES +insulinoma	Total duodeno pancreatectomy	Delayed D250	Yes	Pulmonary embolism, hypercalcemia	Yes	No	Yes
1969 No. 3	Male	43	Antrectomy Vagotomy	ZES + pNET	GI bleeding + ZES + pNET	Total gastrectomy + left pancreatectomy	Operative D21	Yes	Ulcus perforation, GI bleeding	No	No	No
1969 No. 4	Female	40	Total Gastrectomy	ZES + pNET	ZES + pNET	Whipple procedure	Operative D15	Yes	Ulcus perforation	Yes	No	No
1973 No. 5	Female	48	None	ZES + pNET	ZES + pNET	Whipple procedure	Operative D6	Yes	Ulcus perforation, GI bleeding	Yes	No	Yes
1975 No. 6	Male	61	None	ZES + pNET	ZES + pNET	Left pancreatectomy + antrectomy	Operative D10	Yes	Ulcus perforation, GI bleeding.	Yes	No	No
1977 No. 7	Male	55	Left pancreatectomy	ZES + pNET + Insulinoma	Gastric + jejunal ulcers ZES related	Total gastrectomy + jejunal resection	Operative D10	Yes	Ulcus perforation (D2)	Yes	No	Yes
1978 No. 8	Male	40	None	ZES	Perforation of duodenum ZES related	Suture of duodenum + Total gastrectomy	Delayed D330	Yes	Metastatic evolution of gastrinoma	Yes	Yes	No
1978 No. 9	Male	47	None	ZES + pNET	Multiple gastric ulcers ZES-related + pNET	Total gastrectomy + Left pancreatectomy	Delayed D353	No	Work accident	Yes	Yes	No
1982 No. 10	Male	43	None	ZES + pNET	Gastric bleeding ZES related + pNET	Total gastrectomy + Left pancreatectomy	Operative D30	Yes	GI Bleeding	Yes	No	No
1982 No. 11	Male	36	None	ZES + pNET	pNET	Cephalic enucleation	Operative D22	Yes	Intra-abdominal hemorrhage	Yes	No	No
1984 No. 12	Male	54	None	ZES + pNET	pNET	Left pancreatectomy	Delayed D183	Yes	GI Bleeding	Yes	Yes	No
1987 No. 13	Female	68	Duodenal resection	ZES	Perforated ulcer ZES related	Duodenal resection + suture	Operative D8	Yes	Fistula anuria, septic shock	Yes	No	No
1991 No. 14	Male	30	None	ZES	Multiple gastric ulcers ZES related	Antrectomy	Operative D16	Yes	Acute pancreatitis	Yes	Yes	Yes
1997 No. 15	Male	64	Total gastrectomy + enucleation	ZES + pNET	pNET	Left pancreatectomy	Delayed D107	Yes	pNET metastatic evolution	No	No	No
2000 No. 16	Male	77	Total duodenopancreatectomy	ZES + pNET	Biliary stenosis	Stenosis dilatation	Operative D28	Yes	Diabetes, candidosis	Yes	No	No
2003 No. 17	Male	70	Duodenal resection	ZES	Large metastatic node (ZES)	Periduodenal node resection	Operative D7	Yes	Cushing syndrome	Yes	No	Yes
2004 No. 18	Male	65	Left pancreatectomy	ZES + pNET + ECLoma	ECLoma	Total gastrectomy	Delayed D207	Yes	pNET metastatic evolution	Yes	No	Yes

Table 1 continued

Year of death Cohort number	Sex	Age at death	Previous DP surgery	Underlying DP-NET disease	Indication	Surgery	Mortality (day)	MEN1-related death	Cause of death	pHPT	Pituitary adenoma	Adrenal
2008 No. 19	Male	59	Left pancreatectomy		ZES + pNET + Insulinoma	pNET + ZES + Insulinoma	Whipple		procedure		Delayed D150	Yes
Cushing syndrome				Yes	No	Yes						
2010 No. 20	Male	38	Left pancreatectomy	pNETs	pNET	Uncus resection	Operative D5	Yes	Intra-abdominal hemorrhage	Yes	No	Yes
2010 No. 21	Male	64	None	ZES	ZES	Whipple procedure	Operative D5	Yes	Intra-abdominal hemorrhage	Yes	No	No
2010 No. 22	Female	51	Left pancreatectomy	pNET + Insulinoma	pNET	Whipple procedure + right hemicolectomy followed by 2 re surgeries	Operative D17	Yes	Intra-abdominal hemorrhage Septicemia	Yes	Yes	No
2012 No. 23	Male	75	None	pNET	pNET	Left pancreatectomy associated to retroperitoneal liposarcoma resection	Delayed D305	Yes	Liposarcoma recurrence	Yes	No	No
2013 No. 24	Female	41	None	pNET	pNET	Enucleation	Operative D10	Yes	Nephrolithiasis, septic shock	Yes	No	No

possible to analyze trends and update the current understanding of surgical mortality.

However, our work has some limitations. Firstly, the cohort is retrospective among patients included before 1990. Also, the number of patients who died during the year following their GPD-NET resection is limited. Finally, it was not always easy to classify MEN1-related versus non-MEN1-related death because the cause and effect relationship is highly intricate.

The prevalence of ZES-NETs is higher in this series of deceased patients than in follow-up cohorts (70% vs 40% in the GTE cohort of 758 MEN1 patients [8]. Male patients are overrepresented (73% of male patients vs 50% in the GTE cohort). The risk of death was higher among MEN1 men mainly during the first postoperative month. The higher mortality related to male gender can be explained by several factors. First, the penetrance of ZES-NETs, which are at the origin of 83% of this series of deaths, is significantly higher in men (55%) than in women (33%), whereas other GPD-NETs have no gender-related difference. The GTE group already pointed out that in a series of 734 MEN1 patients the prevalence of pancreatic tumors was higher in men than in women (61% vs 54%). This difference was particularly obvious in the ZES-NET subgroup (36.5% vs 24.3%) [16]. Second, estrogen exposure may inhibit GPD-NET growth [17], and women probably have less advanced tumors than men. Male gender seems an independent factor of GPD-NET progression (hazard ratio: 2.22) [18]. Moreover, male gender is a significant predictor of adverse intraoperative and postoperative outcomes in elective pancreatectomy. In a cohort of 22 086 pancreatectomy patients, mortality in male patients was 2.4% compared with 1.6% in female patients (OR = 1.5, $p < 0.001$) whatever the type of pancreatic resection [19]. Moreover, the male fat distribution can cause intraoperative technical difficulties and increase the risk of pancreatic fistula due to fatty pancreas [20].

Ulcer disease due to gastrinoma was the most significant cause of MEN1-related death in historical series [21, 22]. Gastric acid hypersecretion accounted for up to 73–91% of deaths in these early series [9]. Currently, deaths related to uncontrolled gastric acid hypersecretion are rare, demonstrating the effectiveness of long-term medical management of acid hypersecretion. Proton pump inhibitors are the drug of choice for controlling the acid hypersecretion and have almost completely eliminated the lethal complications of peptic ulcer disease [9]. This series confirms that before 1990, 7 out 9 postoperative deaths were related to ulcer perforation or hemorrhage due to poor control of acid secretion. After 1990, there were no deaths related to uncontrolled acid secretion (0% vs 69%). As a result, patients were operated on at a later age because acid secretion was under control. The other causes of death

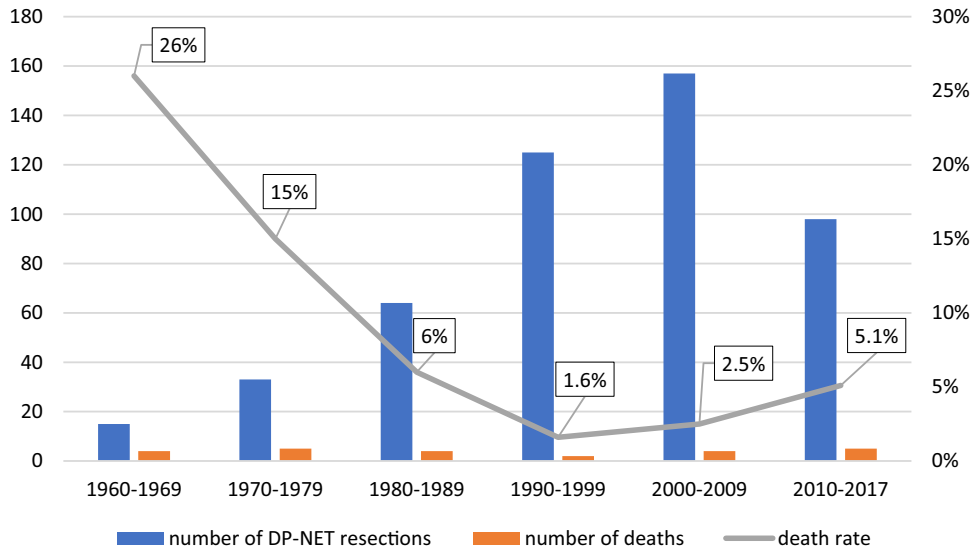

Fig. 2 Evolution of the mortality rate after gastric or duodenopancreatic neuroendocrine tumors (GPD-NET) resection from 1960 to 2017

related to the development of malignant GPD-NETs or other associated MEN1 lesions not related to the digestive tract have become more prevalent (45% vs 8%), as already reported [8]. Another large published series has analyzed the overall causes of death and underscored the responsibility of malignant non-GPD-NETs (83%), excess production of hormones (17%), HPT (9%), thymic or carcinoid tumors (20%), or non-MEN1-related cause such as heart failure (16%), additional non-MEN1 malignancy (25%), or cerebrovascular accident (11%) [9]. Several additional causes, detailed in the 6 particular cases explored in this study, highlight the paramount importance of associated MEN1 lesions which need to be cured or controlled before or during GPD-NET surgery. Septicemia due to nephrolithiasis related to hyperparathyroidism may occur. Cachexia with acute hypercalcemia may favor pulmonary embolism. Indeed, hyperparathyroidism is associated with an increased risk of venous thromboembolism. Two recent studies have shown that patients with primary hyperparathyroidism had high concentrations of hemostatic factors [23, 24]. This hypothesis was reinforced by the prospective follow-up of 27 742 subjects, which found that discordant high serum levels of both calcium and PTH increased the risk of venous thromboembolism when compared with subjects within normal parameters [25]. Severe, uncontrolled Cushing disease is a classic cause of death, and mild ACTH-associated Cushing disease increases the operative risk. Associated liposarcoma close to the pancreatic gland was misleading, and the indication for pancreatic surgery in this case was debatable.

Finally, four patients died from the development of a GPD-NET malignant tumor in the year following the

Table 2 Causes of death

P	Causes of death related to DP-NET surgery			Other MEN1 causes of death (DP-NET excluded) *N* = 5	Non-MEN1 causes of death *N* = 1
N = 24	Surgical technique causes *N* = 5	Medical causes associated with DP-NET surgery *N* = 10	DP-NET metastatic-related mortality *N* = 3		
Operative mortality [0–1 month] *N* = 16	Hemorrhage (*N* = 4) Pancreatitis (*N* = 1)	Acid secretion (*N* = 8) Malnutrition (*N* = 1)		Nephrolithiasis (*N* = 1) Cushing (*N* = 1)	
Delayed mortality [1–12 months] *N* = 8		Acid secretion (*N* = 1)	Loco-regional spread or metastases (*N* = 3)	Pulmonary embolism (hypercalcemia) (*N* = 1) Liposarcoma metastases (*N* = 1) Cushing (*N* = 1)	Work accident (*N* = 1)

Table 3 Trends in surgical indications and in causes of death according to the period

	Before 1990 $N = 13$	1990 and after $N = 11$	p
Mean age of death (years)	47.9 ± 9.5	57.6 ± 15.6	0.09
Operative deaths versus delayed	9/13 (69%)	7/11 (64%)	1
Indications for insulinoma	2/13 (15%)	2/11 (18%)	1
Indications for GDP-NET	11/13 (85%)	8/11 (73%)	0.6
Indications related to ZES (ZES or complications of ZES)	11/13 (85%)	2/11 (18%)	<0.01
Deaths due to lack of acid secretion control	9/13 (69%)	0/11 (0%)	<0.001
Deaths due to other MEN1 lesions (i.e., not related to digestive tract)	1/13 (8%)	5/11 (45%)	0.16

ZES Zollinger–Ellison syndrome, *GPD-NET* gastric, duodenal or pancreatic neuroendocrine tumor

pancreatic surgery. For one, the pancreatic resection should have been considered palliative surgery to control hypergastrinemia. The three other patients died of MEN1-related metastasis a few months after surgery, if liposarcoma is considered a NEM1-related tumor. Therefore, tumor size and aggressiveness and presence of liver metastases have to be considered before surgery. Indication for surgery is debatable when survival prognosis is poor. The most important adverse prognostic factor related to overall survival in MEN1-related GPD-NETs is the presence of liver or other distant metastases [9, 26]. Moreover, a 46-patient GTE prospective study demonstrated that non-functioning PNETs of 2 cm or smaller are associated with a low risk of disease-specific mortality and emphasized the need for a benefit/risk assessment before a pancreatic resection [26].

Conclusion

This study is original in the sense that it focuses on MEN1 mortality with resected pancreatic or gastric NETs. It demonstrated both the importance of the surgical act and of the control of secretory syndromes. Acid secretion can now be controlled effectively, but any abnormalities in calcium, cortisol or insulin metabolism may still carry increased risks of morbidity and mortality. As a consequence, these two elements are the two main causes of death in MEN1 patients with pancreatic resection. Despite the diagnostic and therapeutic advances of the 1990s, in view of the results of this study, it should be considered necessary to carry out a strict evaluation of the pancreatic secretory syndrome but also of the other involvement, particularly parathyroid. It will also be essential to evaluate tumor resectability in order to improve the surgery conditions and thus patient prognosis. GPD-NET tumor resection should always be discussed because postoperative adverse events do not appear to impact the oncologic outcome of NEM1 patients [27]. To conclude, the management of MEN 1 patients with pancreatic involvement must include a "patient pathway" with multidisciplinary management. A complete diagnosis of all MEN1 lesions has to be done. Medical and/or surgical acts must be individualized and carefully timed. Hyperparathyroidism and Cushing syndrome need to be controlled before GPD-NET surgery can be considered appropriate.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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