One-year operative mortality in MEN1 patients operated on gastric and duodeno-pancreatic Neuro Endocrine Tumors. An AFCE and GTE cohort study.

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Abstract (A refaire en dernier)

Introduction

20 to 70% Multiple Endocrine Neoplasia type 1 (MEN 1) have pancreatic involvement. Prognosis is reserved. Middle age at death is 54 years old. The aim of this work was to analyze causes of death of MEN1 patients with pancreatic involvement.

Material and methods

Analysis of deaths has been executed from 1220 patients of GTE cohort. Only patients with pancreatic involvement and died after surgery have been included. Extraction of data has been done in January 2016. Analysis took into account delay between surgery and death (post operative deaths [<1month after surgery] versus delayed deaths [beyond 1 year after surgery]) and the period (death before 1990 vs after 1990).

Results

30 patients MEN1 died with pancreatic involvement (20 men). 28 deaths were linked to MEN1 (2 accidental deaths) and 12 occured before1990. Middle age was 50 years old (29-76 years old). Four deaths were attributable to the evolution of extra pancreatic involvement (pituitary gland 3, liposarcoma 1). 20/28 had hypergastrinemia. 12/28 deaths were due to a metastatic evolution (gastrinoma 9, insulinoma 3). Before surgery, secretory syndrome was not controlled in any patient before 1990 vs 50% after 1990. There were 15/28 postoperative

deaths or during hospitalization. 8/15 were due to a hemorrhage shock (2 cephalic duodenopancreatectomy, 2 enucleations, 4 left pancreatectomies). 3/15 deaths were due to a septic shock (2 peritonitis by perforation, obstructive pyelonephritis). Before 1990, there were 9/12 postoperative deaths, without secretory control, and 1 death linked to surgery. After 1990, 6/16 patients had not secretory control (including 1 primary hyperparathyroidy (PPH) uncontrolled at the origin of a refractory septic shock) - 2 patients died of a hemorrhage shock and 3 deaths of surgery.

Conclusion

Surgery and the non-control of secretory syndrome remain the 2 main causes of death of MEN 1 patients operated of a pancreatic neuroendocrine tumor (NET). Improvement of prognosis of these patients requires a strict evaluation of secretory syndrome and tumor resectability before pancreatic surgery.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant and inherited disease that predisposes carriers to various neuro endocrine tumors (NET). The criteria for diagnosis were established first in Gubbio during the Seventh International Workshop on MEN held during 1999 in Italy (Brandi et al., 2001) and then regularly updated (Brandi et al., 2001; Marini et al., 2006; Thakker et al., 2012). MEN1 is related to mutations in the MEN1 gene, a gene of approximately 10-kb that encodes for menin and is located on chromosome 11q13 (Agarwal et al., 1997; Chandrasekharappa et al., 1997; Lemmens et al., 1997). Duodeno-pancreatic NETs **(**DP-NETs) represent the second most frequent MEN1 associated lesion after hyperparathyroidism and are responsible for the majority of MEN1 cancer-related deaths (Brandi, 2000; Goudet et al., 2010a; Ito et al., 2013a). The three main usually associated secretions are gastrin, responsible for Zollinger-Ellison Syndrome (ZES), insulin and glucagon. Indications for surgery for MEN1-related DP-NETs aim at controlling insulin and less frequently glucagon or VIP secretion, or at preventing metastatic spread in case of large non functional DP-NETs. Operative mortality after duodeno pancreatic resection is well known and remains as high as 5,7% and 8,1% respectively at 30 days and 90 days in a recent multicentric study (Farges et al., 2017). These results indicate that operative mortality of DP-NET must be evaluated on a several months period of time. Moreover, particular operative deaths may occur in MEN1 patients. They may be related to other associated MEN1 lesions which interfere with the operative course either because of their own secretion or because of their own metastatic behavior (Goudet et al., 2010a)(Ito et al., 2013a). Therefore, the aim of this study was to analyze the overall operative causes of mortality in MEN1 patients with DP-NET one a one-year after surgery using the MEN1 GTE cohort (Groupe d'étude des Tumeurs Endocrines) which is deemed to be representative of the MEN1 disease and which is regularly used to assess care practices.

PATIENTS AND METHODS

MEN1 patients.

The study population was composed of symptomatic MEN1 patients registered in the GTE [Groupe des Tumeurs Endocrines, (GTE)] database. The purpose of this network, created in February 1991, is to maintain a registry of NEM1 patients at the Center for Epidemiology of

the Population at the University of Bourgogne in Dijon, France, receiving reports from 5 French and Belgium genetics departments accredited for genetic testing of MEN1 and also from primary care physicians. Registry data include results of genetic testing, clinic visit reports, operative reports, pathology reports, and hospital discharge summaries (Goudet et al., 2010). 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 fir 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 operated on pancreas, duodenum or stomach from June 1956 to November 2017 and who deceased during the first postoperative year were included in the study. Indication for surgery must have been directly or indirectly due to a MEN1 related NET of the duodenum, the pancreas or the stomach. Patients who died after hepatic surgery for the cure of associated metastases were not included in the study. Precise causes of death were analyzed. The analysis took into account the delay between surgery and death (< 1 month after surgery [operative mortality] and during the following months during the first year after surgery [delayed operative mortality]), the period of time (until 1990 versus after 1990). Causes of death were classified as follows: 1-related to pancreatic, duodenal and gastric surgery (a- due to technical cause b-due to medical associated causes c-due to metastases) 2- related surgeries on other MEN1 lesions 3- related to no-MEN1 causes. Patients for whom delay between pancreatic resection date and death was more than 1 year, were excluded.

Statistical analysis

Comparisons between groups were made using Fisher exact tests for categorical variable and using non parametric tests for continuous variables. *P* values < 0.05 were considered statistically significant. Statistical analyses were performed with Stata software (*ref).*

RESULTS

One-thousand-two-hundred-and-twenty patients were included in the GTE cohort at the time of the study (November 2017). Twenty-four patients fulfilled the mortality inclusion criteria (2.0%). There were 19 men (79%) and 5 women (21%). Mean (mettre médiane) age at death

was 52.4 years (mini: 30 – maxi: 77). Clinical data of patients who died during the first year post operatively are displayed Table 1. ZES was found in 20 patients (83%), insulinoma in 4 (17%)], ECLoma in one (4%). Twenty-two patients had a diagnosis of hyperparathyroidism (92%), 5 a diagnosis of pituitary adenoma (21%), and 9 of adrenal NET (37%). Sixteen deaths occurred in the operative period (67%) versus 8 deaths in the delayed period (33%). Causes of deaths are displayed Table 2. Only one case seemed not to be related to MEN1 disease (work accident). Five deaths (21%) were due to/associated with MEN1 defavourable conditions which were not related to DP-NETs. Hyperparathyroidism was involved in 2 of them: **Case 1236** was a 41-year old woman operated in 2013 on a 2-cm non-functional pancreatic NET by enucleation. Surgery was followed by an hypovolemic shock. A bleeding splenic artery was responsible for an intraabdominal hemorrhage which was radiologically and successfully embolized. A pyelonephritis occurred during a short oliguria period. The patient died from septicemia and septic shock. Pyelonephritis was a direct result of an underlying nephrolithiasis associated to non operated hyperparathyroidism. Pathological report of the tumor showed a 2 cm benign NET with a Ki67 <1%. **Case 238** was operated on in 1965 for multiple DP-NETs (3 insulinomas of 3, 1.5 and 1 cm) by total duodenopancreatectomy without knowing the MEN1 underlying disease. Calcemia increased progressively post operatively and reached 128mg/l. Anorexia, cachexia, phlebitis and and finally pulmonary embolism occurred. The MEN1 diagnosis was established retrospectively. **Case 473** was operated on a 2.5x2cm peri duodenal node. Immunostaining was positive for gastrin. A frank Cushing syndrome hardly manageable under medical treatment was present. A 6 cm right adrenal was removed during the same surgery. The patient died from metabolic complications due to Cushing syndrome. **Case 526** was suffering from a longstanding ACTH-dependant Cushing syndrome under Somatuline but Free Urinary Cortisol was still elevated. Both adrenals were enlarged. The patient was first operated on by left pancreatectomy for insulinoma several years before. Whipple procedure was secondary carried out for a 45 mm cephalic NET. A secondary diabetes due to total pancreatectomy associated to Cushing syndrome was difficult to manage and the patient died from epilepsy without any brain metastasis. **Case 1164** was a 75-year old man NEM-1, 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 of the tumor showed 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 his liposarcoma. This death was not DP-NET related.

Three patients (12%) died beyond the first postoperative month from a distant metastases from there DP-NET. Trends in surgical indications and in causes of death according to the period of time (until 1990 versus after 1990), are described Table 3. Mean age at death increased from 48 to 58 years old. Deaths related to uncontrolled acid secretion disappeared after 1990 while deaths related to associated MEN1 lesions increased, from 8% before 1990 to 45% after 1990. Indications for duodeno-pancreatic resection decreased for ZES whereas they did not change for other tumors.

DISCUSSION

This is the first study analyzing operative deaths following resection of duodenal pancreatic or gastric NETs in MEN1 patients whatever the indication for surgery. Indeed, already published data were focused on MEN1 patients operated on non-functioning DP-NET. They have already shown that the risk of postoperative Clavien-Dindo grade III to IV complications reaches 33% (Nell et al., 2018). This new present study shows that one-third of "operative" deaths occurred after the one-month operating period during the first year after surgery and that men and Zollinger-Ellison syndrome were over represented. As anticipated, surgery for DP-NETs and gastric NETs are directly responsible for the majority of operative deaths. Nevertheless, other causes of deaths exist and are more frequently due to medical associated conditions or other MEN1 lesions (63%) than to usual well-known complications of pancreatic surgery (21%).

Several particular aspects of this study deserve to be highlighted: 1- Indeed all the various causes of deaths occurring during the first postoperative year were analyzed. Analyzing deaths only in the first postoperative month would have underestimated the death rate and would have not emphasized enough the importance of other deaths due to tumor aggressiveness occurring rapidly during the following months. 2- The large size GTE-cohort of 1220-patient is deemed to be representative of MEN1 disease, of its natural history, of the various treatments used and of their complications. 3- The study time covers a 5-decade period and makes possible trends analyzes and up-dated conclusions regarding today surgical mortality. However, our work has some limitations since the cohort is retrospective among patients included before 1990. The number of patients who died during the year following their DP-NET resection is limited. It was not always easy to classify MEN1 versus non-MEN1 related death since many causes may be intricated.

ZES-NETs prevalence is higher in this series of deceased patients than in follow-up cohorts (70% vs 40% in the GTE cohort of 758 MEN1 patients (Goudet et al., 2010)). Male patients are over-represented (73% of male patients versus 50% in the GTE-cohort). The risk of death was higher among MEN1 men mainly during the first postoperative month. This mortality related to male gender can be explained by several factors. First, the penetrance of ZES-NETs is significantly higher in men (55%) when compared with women (33%) while other DP-NETs do not show any gender related difference. Indeed ZES-NETs represent 83% of this mortality series. The GTE group already pointed out in a 734-patients MEN1 series that the prevalence of pancreatic tumors was higher in men than in women (61% versus 54%). This difference was particularly obvious in the subgroup of ZES-NETs (36,5% versus 24,3%) (Goudet et al., 2011). Second, estrogen exposure may inhibit DP-NET growth (Qiu et al., 2017) and women probably have less advanced tumors than men. Male gender seems an independent factor of DP-NET progression (HR 2,22) (Giudici et al., 2017). Moreover male gender is a significant predictor of adverse intraoperative and postoperative outcomes in elective pancreatectomy. Mortality among male patients was 2,4% compared to 1,6% among female patients (OR = 1,5, p < 0,001) whatever the type of pancreatic resection in a cohort of 22 086 patients who had had a pancreatectomy (Mazmudar et al., 2017).

From 1990, the control of acid secretions ~~control~~ has changed the prognosis of patients operated on from a DP-NET or a gastric-NET. ~~In historical series,~~ Ulcer disease due to gastrinoma was the most important cause of MEN1-related death in historical series (Ballard et al., 1964)(Pieterman et al., 2014). ~~In these early series,~~ Gastric acid hypersecretion accounted for up to 73-91% of deaths in these early series (Ito et al., 2013). Currently, deaths related to uncontrolled gastric acid hypersecretion ~~is~~ are rare, ~~that~~ 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 has completely eliminated the lethal complications of peptic ulcer disease (Ito et al., 2013). ~~In our series,~~ This series shows that before 1990, 7 out 9 postoperative deaths were related to ~~an~~ ulcus perforation or ~~an~~ hemorrhage ~~due to~~ by lack of acid secretion control. After 1990, ~~the evolution of pancreatic tumors is delayed by~~

~~proton pump inhibitors,~~ patients ~~are~~ were operated at a later age since acid secretion was under control by PPIs ~~and~~ . Deaths related to ~~an~~ ulcus perforation or ~~a~~ GI bleeding have disappeared (0% vs 69%) in favor of deaths related to the evolution of a malignant DP-NET or other MEN1 lesions (45% vs 8%), as already reported by other authors (Goudet et al., 2010).

~~In his large series, Ito found that, at present,~~ Another large published series analyzing the overall causes of deaths have pointed out the responsibility of ~~deaths were due to another MEN1-related deaths as~~ malignant non-DP-NET (83%), ~~any~~ hormone excess state (17%), HPT~~-related~~ (9%), thymic or carcinoid tumors ~~related~~ (20%), or ~~to~~ non-MEN1-related cause, as cardiac failure (16%), additional non-MEN1 malignancy (25%), or cerebrovascular accident (11%) (Ito et al., 2013a). ~~In our series,~~ Several additional causes were found in the present study mainly during the first postoperative year, such as uncontrolled severe Cushing, malnutrition, nephrolithiasis, or pulmonary embolism. ~~We considered~~ Pulmonary embolism may be considered as a MEN1-related cause. Indeed, hyperparathyroidism is associated with an increase of venous thromboembolism risk. Two recent studies ~~had~~ have shown that patients with primary hyperparathyroidism had high concentration of hemostatic factors (Erem et al., 2008)(Erem et al., 2009). This hypothesis was reinforced by the prospective follow-up of 27 7842 subjects, which found that ~~discordant~~ high serum levels of both calcium and PTH increased risk of venous thromboembolism when compared to subjects with these two normal parameters, or one of two high isolation **(pas clair)** (Lerstad et al., 2017).

~~In our series,~~ Four patients died from the evolution of their DP-NET malignant tumor in the year following the pancreatic surgery ~~of due to the evolution of their DP-NET malignant tumor~~. For one, the pancreatic resection should be considered as a palliative surgery, with the aim of controlling hypergastrinemia which was un-controlled by medical treatment. The 3 other patients died of their MEN1-related metastasis a few months after surgery, considering that liposarcoma was a NEM1-related tumor. Therefore size and aggressiveness of the tumor, presence of liver metastasis ~~and aggressiveness of the DP-NET tumor~~ 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 DP-NETs is the presence of liver or other distant metastasis (Triponez et al., 2017)(Ito et al., 2013). Moreover, a 46-patient GTE prospective study ~~Triponez et al shown~~, ~~on a prospective series of 46 P-NET~~

~~MEN1 patients~~ demonstrated that nonfunctioning P-NETs of 2 cm or smaller ~~is~~ are associated with a low-risk of disease specific mortality and emphasized the need for a benefit/risk assessment before a pancreatic resection (Triponez et al., 2017)

At least, we considered the work accident as non-MEN1 related, because we had no information on the exact circumstances of this accident. Finally, several deaths have been attributed to uncontrolled hypersecretions (insulin dysregulation, hyperparathyroidism, Cushing) that may not have been directly responsible for the death but were a factor contributing to the patients' frailty.

Conclusion

This study is an original one in the sense that it focuses on MEN 1 mortality with resected pancreatic or gastric NETs ~~involvement~~. It demonstrated both the importance of the surgical act and of the control of any secretory syndrome ~~uncontrol~~. Acid secretion is now correctly controlled but any abnormality of calcium , cortisol or insulin metabolism may still carry its own morbidity and mortality. As a consequence, these two elements represent the two main causes of deaths of MEN1 patients with pancreatic resection. Despite diagnostic and therapeutic advan

ces of the 90s, in view of the results of this study, it will be necessary from now to carry out a strict evaluation of the pancreatic secretory syndrome but also of the other involvements in particular parathyroid. It will also be essential to evaluate the tumor resectability to improve the operative indications and thus the prognosis of the patient. To conclude, the management of MEN 1 patients with pancreatic involvement must include « a patient pathway » with multidisciplinary management. A complete diagnosis report has to be done. Medical and / or surgical therapeutic acts must be adapted individually and temporally.

Finally, patients who had a who were resected for PET ZES resected had a higher risk to die in the long run at long term (71% versus 29% for no resection) (Ito et al., 2013).

Table 1.

Clinical data related to patients who died from any surgical procedure during the first year post operatively.
N=24

Year of death *Cohort number*	Sex	Age at death	Previous DP surgery	Underlying DP-NET disease	Indication	Surgery	Mortality	MEN1 related death	Cause of death	pHPT	Pituitary adenoma	Adrenal
1961 *N°134*	Male	50	None	ZES + pNET	pNET + ZES	Left pancreatectomy	Operative	Yes	Ulcus perforation	Yes	No	Yes
1965 *N°238*	Male	38	None	ZES + pNET + Insulinoma	Multiple pNETs + insulinoma	Total duodeno pancreatectomy	Delayed	Yes	Pulmonary embolism, hypercalcemia	Yes	No	Yes
1969 *N°517*	Male	43	Antrectomy Vagotomy	ZES + pNET	GI bleeding + ZES + pNET	Total gastrectomy + left pancreatectomy	Operative	Yes	Ulcus perforation, GI bleeding	No	No	No
1969 *N°359*	Female	40	Total Gastrectomy	ZES + pNET	ZES + pNET	Whipple procedure	Operative	Yes	Ulcus perforation	Yes	No	No
1973 *N°454*	Female	48	None	ZES + pNET	ZES + pNET	Whipple procedure	Operative	Yes	Ulcus perforation, GI bleeding	Yes	No	Yes
1975 *N°562*	Male	61	None	ZES + pNET	ZES + pNET	Left pancreatectomy + antrectomy	Operative	Yes	Ulcus perforation, GI bleeding.	Yes	No	No
1977 *N°126*	Male	55	Left pancreatectomy	ZES + pNET + Insulinoma	Gastric + jejunal ulcers	Total gastrectomy + jejunal resection	Operative	Yes	Ulcus perforation (D2)	Yes	No	Yes
1978 ***N°1073***	Male	40	None	ZES	Perforation of duodenum	Suture of duodenum + Total gastrectomy	Delayed	Yes	Metastatic evolution of gastrinoma	Yes	Yes	No
1978 *N°816*	Male	47	None	ZES + pNET	Multiple gastric ulcers + pNET	Total gastrectomy + Left pancreatectomy	Delayed	No	Work accident	Yes	Yes	No
1982 ***N°13***	Male	43	None	ZES + pNET	Gastrig bleeding + pNET	Total gastrectomy + Left pancreatectomy	Operative	Yes	GI Bleeding	Yes	No	No
1982 ***N°3***	Male	36	None	ZES + pNET	pNET	Cephalic enucleation	Operative	Yes	Intra abdominal hemorraghae	Yes	No	No
1984 *N°59*	Male	54	None	ZES + pNET	pNET	Left pancreatectomy	Delayed	Yes	GI Bleeding	Yes	Yes	No
1987 *N°1*	Female	68	Duodenal resection	ZES	Perforated ulcer	Duodenal resection + suture	Operative	Yes	Fistula Anuria, septic shock	Yes	No	No

1991 *N°8*	Male	30	None	ZES	Multiple gastric ulcers	Antrectomy	Operative	Yes	Acute pancreatitis	Yes	Yes	Yes
1997 *N°5*	Male	64	Total gastrectomy + enucleation	ZES + pNET	pNET	Left pancreatectomy	Delayed	Yes	pNET metastatic evolution	No	No	No
2000 *N°51*	Male	77	Total duodeno pancreatectomy	ZES + pNET	Biliary stenosis	Biliary drainage	Operative	Yes	Denutrition, diabetes, candidosis	Yes	No	No
2003 *N°473*	Male	70	Duodenal resection	ZES	Large metastatic node	Periduodenal node resection	Operative	Yes	Cushing syndrome	Yes	No	Yes
2004 *N°1259*	Male	65	Left pancreatectomy	ZES + pNET + ECLoma	ECLoma	Total gastrectomy	Delayed	Yes	pNET metastatic evolution	Yes	No	Yes
2008 *N°526*	Male	59	Left pancreatectomy	ZES + pNET + Insulinoma	pNET + Insulinoma	Whipple procedure	Delayed	Yes	Cushing syndrome	Yes	No	Yes
2010 *N°1081*	Male	38	Left pancreatectomy	pNETs	pNET	Pancreatic head resection	Operative	Yes	Intra abdominal hemorraghae	Yes	No	Yes
2010 *N°241*	Male	64	None	ZES	ZES	Whipple procedure	Operative	Yes	Intra abdominal hemorraghae	Yes	No	No
2010 *N°253*	Female	51	Left pancreatectomy	pNET + Insulinoma	pNET	Whipple procedure + right hemicolctomy	Operative	Yes	Intra abdominal hemorraghae	Yes	Yes	No
2012 *N°1164*	Male	75	None	pNET	pNET	Left pancreatectomy associated to retroperitoneal liposarcoma resection	Delayed	Yes	Liposarcoma reccurrence	Yes	No	No
2013 *N°1236*	Female	41	None	pNET	pNET	Enucleation	Operative	Yes	Nephrolithiasis, septic shock	Yes	No	No

Table2.
Causes of deaths

P N=24	Causes of death related to DP-NETs'surgery, Surgical technique causes N=5	Medical causes associated to DP-NET surgery N=10	DP-NET Metastatic related mortality N=3	Other MEN1causes of mortality (DP-NET excluded) N=5	Non MEN1 causes of mortality N=1
Operative mortality [0 to one 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 to 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	13/13 (100%)	7/11 (64%)	0.03
Deaths due 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

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