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**Impact de la normalisation précoce de la gastrinémie postopératoire sur la survie à long terme après traitement chirurgical du gastrinome.**

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# Abréviations

## En français

| *Abréviations* | *Signification* |
|---|---|
| NNE | Néoplasie neuroendocrine |
| SZE | Syndrome de Zollinger-Ellison |
| NEM1 | Néoplasie Endocrinienne Multiple de type 1 |
| GJ | Gastrinémie sérique à jeun |
| IPP | Inhibiteurs de la pompe à protons |

## En anglais

| *Abbreviations* | *Signification* |
|---|---|
| ZES | Zollinger-Ellison Syndrome |
| FSG | Fasting Serum Gastrin |
| MEN1 | Multiple Endocrine Neoplasia type 1 |
| PPIs | Proton Pump Inhibitors |
| AST | Antisecretory therapy |
| SST | Secretin Stimulation Test |
| EUS | Endoscopic Ultrasound |

| | |
|---|---|
| CT | Contrast-enhanced computed Tomography |
| MRI | Magnetic Resonance Imaging |
| PET | Positron Emission Tomography |
| OS | Overall Survival |
| KM | Kaplan-Meier |

## Table des matières

## Introduction Générale:

Le Syndrome de Zollinger-Ellison (SZE), décrit pour la première fois en 1955 par Robert Zollinger et Edwin Ellison, est un ensemble de manifestations cliniques rares liées à une tumeur appelée gastrinome, appartenant à la famille des néoplasies neuroendocrines fonctionnelles, qui sécrète un peptide, la gastrine. Cette hypersécrétion hormonale autonome de gastrine entraîne une hyperproduction d'acide gastrique, responsable d'ulcères multiples, récidivants et atypiques associés à des douleurs abdominales, des diarrhées chroniques, constituant les manifestations classiques du SZE (1,2).

Le gastrinome est une lésion rare, avec une incidence annuelle estimée entre 0,1 et 3 cas par million d'habitants et dont le potentiel malin est rapporté dans 60 à 90% des cas (3–5).

Le gastrinome peut survenir de manière sporadique ou dans le cadre de syndrome héréditaire génétiquement déterminé tel que la Néoplasie Endocrinienne Multiple de type 1 (NEM1) dans 20 à 25% des cas (6).

Longtemps considérés comme d'origine pancréatique, il est aujourd'hui démontré que la principale localisation concerne le duodénum, avec des proportions variant de 45 à 100% (7–9) selon les séries.

Dans sa forme sporadique la plus commune, il s'agit d'une lésion unique de la paroi du deuxième duodénum qui siège dans la sous-muqueuse et mesurant le plus souvent moins de 1 cm, ce qui rend difficile la détection pré ou peropératoire.

Certaines études ont également suggéré l'existence de gastrinomes ganglionnaires primitifs, sans lésion d'organe retrouvée (10), bien que cette définition reste débattue d'un point de vue oncologique et histologique.

Sur le plan biologique, le dosage de la gastrinémie à jeun à distance de la prise d'IPP constitue un excellent test de dépistage en raison de sa grande sensibilité. Cependant, une gastrinémie à jeun élevée isolée nécessite d'être associée à une augmentation de la sécrétion d'acide gastrique mesurée lors d'une épreuve de tubage gastrique pour confirmer le diagnostic, examen de plus en plus difficile d'accès (7). L'imagerie de localisation des lésions primitives et secondaires et notamment l'imagerie fonctionnelle aux récepteurs de la somatostatine jouent un rôle fondamental dans la prise en charge chirurgicale du gastrinome. Plus de 90% des gastrinomes sont histologiquement bien différenciés et expriment ces récepteurs, en particulier le sous-type 2 (SSTR2), établissant l'imagerie des récepteurs de la somatostatine, historiquement la scintigraphie à l'octréotide puis plus récemment la Tomographie par Émission de Positon TEP au 68Ga-DOTA-TOC (ou -NOC, ou -TATE) comme l'outil diagnostique et de suivi de référence (11,12).

Le traitement du SZE repose sur deux axes : le contrôle de l'hyperacidité gastrique, aujourd'hui efficacement maitrisé par les IPP, et le traitement curatif de la tumeur. Ce dernier est essentiel du fait du risque de métastases hépatiques, principal facteur pronostique (13,14). La chirurgie curative, lorsqu'elle est possible, est recommandée par les experts, bien que son indication reste plus controversée dans les formes associées à la NEM 1.

De nombreuses séries ont souligné l'intérêt de l'exploration chirurgicale systématique, même en l'absence de lésions visibles en imagerie préopératoire et l'utilisation de l'endoscopie peropératoire avec transillumination ainsi que la palpation

bidigitale duodénale lors de la duodénotomie peropératoire systématique introduite par N. Thompson en 1989 (15) a permis d'augmenter le rendement de la détection peropératoire de ces lésions. La mesure de la gastrinémie en peropératoire, et sa variation après résection de la ou des lésions associées au test de stimulation à la sécrétine, lorsqu'il était disponible, permet ainsi d'apprécier la qualité de la résection chirurgicale.

Peu d'études se sont intéressées à la cinétique de la gastrinémie mesurée à jeun après la chirurgie, notamment la normalisation précoce du taux de gastrine dans le premier mois postopératoire, et l'association éventuelle de ce dernier paramètre avec la survie globale à long terme n'est pas connue.

C'est dans ce contexte, que nous avons mené cette étude, visant à évaluer l'association entre la normalisation précoce de la gastrinémie à jeun dans le mois suivant la chirurgie à visée curative du gastrinome, et la survie globale à 20 ans chez les patients atteints de SZE pris en charge au CHU de Lille.

Cette étude repose sur une collection historique de patients atteints du syndrome de Zollinger-Ellison suivis au CHU de Lille, initiée par le Professeur Charles PROYE (1938–2007), pionnier de la chirurgie endocrinienne en France, puis poursuivie par son successeur, le Professeur François PATTOU. Elle s'inscrit dans la continuité d'un travail mené par plusieurs générations d'internes en chirurgie, dont les travaux ont contribué à documenter et enrichir la compréhension de cette pathologie rare. C'est avec un profond respect pour cet héritage scientifique et clinique que nous avons entrepris cette nouvelle analyse, dont l'objectif est d'apporter une contribution supplémentaire à l'amélioration de la prise en charge du SZE.

# Postoperative serum gastrin levels and overall survival following surgical treatment of Gastrinoma


## Abstract

***Objective:*** Zollinger-Ellison syndrome (ZES) is a rare neuroendocrine disorder caused by gastrin-secreting neuroendocrine tumors (gastrinomas), leading to gastric acid hypersecretion and recurrent peptic ulcers. Although surgery is the only curative treatment, reliable early postoperative prognostic markers are lacking. We aimed to assess whether normalization of fasting serum gastrin (FSG) within the first postoperative month is associated with the 20-year overall survival.

***Patients and Methods:*** This retrospective single-center cohort study included all adult patients who underwent curative-intent surgery for Zollinger-Ellison syndrome (ZES) at Lille University Hospital between 1985 and 2024. Patients with histologically confirmed gastrinoma and available fasting serum gastrin (FSG) measurements were eligible for analysis. The exposure of interest was postoperative FSG normalization, defined as a level ≤120 pg/mL measured within the first postoperative month. The primary outcome was the 20-year overall survival, estimated using the Kaplan–Meier method. Patients were stratified by postoperative gastrin normalization. Survival was compared using Kaplan–Meier analysis with log-rank test, and Cox regression adjusted for age and clinical status (Multiple Endocrine Neoplasia type 1-associated ZES vs. sporadic).

***Results**:* Among the 95 patients included in the analysis, [median age 55 (IQR 44-64) years - 44 female (46%)], 69 (73%) achieved FSG normalization within the first postoperative month. The overall survival (OS) rate for the entire cohort was 82% (95% CI 71-89) at 10 years and 49% (95% CI 36-61) at 20 years. The overall survival was significantly improved in patients with postoperative FSG normalization, with 10-year and 20-year survival rates of 89% (95% CI 77-95) and 59% (95% CI 44-72) compared to 60% (95% CI 34-78) and 17% (95% CI 3-42) in those who did not achieve normalization: adjusted HR 0.30 (95% CI, 0.14-0.63; p = 0.0016). This association was independent of patient age at the time of surgery and whether the disease was sporadic or MEN1-associated.

***Conclusions**:* Normalization of fasting serum gastrin within the first postoperative month following curative-intent surgery for Zollinger-Ellison syndrome–related gastrinomas was independently associated with improved overall survival. This early biochemical response could serve as a valuable prognostic marker and should be validated in prospective studies and external cohorts.

## Introduction:

Zollinger-Ellison syndrome (ZES), first described in 1955 by Robert Zollinger and Edwin Ellison (1), is a rare but challenging condition caused by secreting neuroendocrine neoplasms, i.e. gastrinomas, leading to gastric acid hypersecretion and resulting in recurrent peptic ulcers, abdominal pain, and chronic diarrhea (2–4).

ZES can occur sporadically or in the context of hereditary syndromes, particularly multiple endocrine neoplasia type 1 (MEN1) in approximately 20-25% of cases (5).

While gastrinomas were long thought to be primarily pancreatic lesions, they are now most frequently found in the duodenum, with proportions ranging from 45 to 100% (2,6,7). Notably, approximately 60 to 90% of gastrinomas are located within the so-called “gastrinoma triangle” (also named Passaro’s triangle) (8–11).

While acid suppression and thus the control of symptoms has been significantly improved by proton pump inhibitors (PPIs) (12–14), control of gastrin secretion remains achievable only through surgical resection of the gastrin-secreting tumors, which is the only potential option for long-term disease control and improved survival in localized disease. In metastatic gastrinomas, however, gastrin secretion and disease progression may be controlled using somatostatin analogs, liver-directed therapies, chemotherapy, or peptide receptor radionuclide therapy (PRRT).

Thus, current surgical guidelines (11,15,16) advocate for tumor resection whenever feasible, particularly in sporadic gastrinomas. In contrast, surgical management in MEN1-associated cases remains more controversial, largely due to the frequent presence of multiple small duodenal gastrinomas, which often complicate complete resection and contribute to heterogeneous long-term outcomes (15,17–21).

Despite recent imaging advances for preoperative localization (22,23), reliable early postoperative markers to predict long-term prognosis are still critically needed. In

clinical practice, the follow-up primarily relies on fasting serum gastrin (FSG) levels, which serve as an indirect marker of tumor activity and surgical success.

Although gastrin monitoring is clinically relevant for the long-term follow-up to assess disease control and detect recurrence, the early postoperative kinetics of FSG, particularly in the days and weeks following surgery, remain poorly characterized (24,25). The prognostic significance of fasting serum gastrin normalization following surgery remains unclear and its impact on long-term survival is still unknown.

Based on a single-center French cohort, this study aimed to evaluate whether normalization of FSG within the first postoperative month is associated with improved long-term overall survival in patients with Zollinger-Ellison syndrome treated by surgical resection of gastrinomas.

## Patients and methods

*Study design, participants and definitions*

This retrospective, single-center, observational cohort study was designed to investigate the association between postoperative normalization of FSG levels within the first month following curative surgery and 20-year survival in patients with Zollinger-Ellison syndrome-associated gastrinomas.

All adult patients with a clinical and/or biochemical, and/or imaging diagnosis of ZES, who underwent curative-intent surgery at the Department of General and Endocrine Surgery at Lille University Hospital, between January 1985 and November 2024 were consecutively included in the present study.

Patients were excluded if i) the diagnosis of ZES-related gastrinomas could not be confirmed through pathological analysis and/or without immunohistochemical staining for gastrin ii) or if postoperative FSG levels were missing or uninterpretable. Clinical, biochemical, imaging, surgical and pathological data were retrospectively collected from electronic and paper-based medical records.

Gastrinoma diagnosis was based on a combination of clinical symptoms and/or biochemical criteria and/or positive imaging.

*Clinical symptoms* including abdominal pain, chronic diarrhea and a history of peptic ulcers.

*Biochemical diagnosis of* ZES*,* including hypergastrinemia and, when available, elevated gastric acid output and/or a positive secretin stimulation test (SST).

Hypergastrinemia was defined by FSG > 120 pg/ml, preferably measured off antisecretory therapy (AST), including proton pump inhibitors (PPIs), and when applicable, somatostatin analogs. When treatment status at the time of measurement

was unknown, patients were considered to be on antisecretory therapy by default. In patients with multiple available preoperative values, the lowest value was retained for analysis.

Gastric acid output measurement, performed via nasogastric tube at least 24 hours off antisecretory therapy, with basal acid output > 15 mEq/h considered abnormal (or > 5 mEq/h in patients with chronic hypo- or achlorhydria).

A secretin stimulation test was frequently performed. SST was performed off AST and was defined as an increase in gastrin levels >120 pg/mL above baseline following intravenous administration of 2 IU/kg of secretin (Δ gastrin [SST – FSG] >120 pg/mL).

*Imaging* diagnosis of gastrinomas was performed using evolving techniques over time, including selective angiography, endoscopic ultrasound (EUS), contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), somatostatin receptor scintigraphy with octreotide (OctreoScan®), positron emission tomography (PET) — notably with 18F-FDG and, more recently, 68Ga-DOTATOC.

We have defined three distinct eras based on technological advancements. Era 1 from January 1985 to June 1991, characterized by anatomical imaging and absence of functional imaging. Era 2 from July 1991 to July 2018, marked by the introduction of scintigraphy functional imaging using OctreoScan® and Era 3 since August 2018 marked by the introduction of PET imaging using 68Ga-DOTATOC/CT.

Association with MEN1 was defined according to established clinical criteria: the presence of at least two of the three main MEN1-associated endocrine tumors (parathyroid, pituitary, and/or pancreatic), or the presence of one such tumor in addition to a first degree relative with genetically confirmed MEN1, regardless of whether a genetic mutation was confirmed.

Preoperative patient characteristics (sex, age, body mass index in $kg/m^2$, history of tobacco use, type 2 diabetes, MEN1 status, history of hyperparathyroidism, pituitary adenoma, parathyroidectomy, diagnostic delay defined as the time from initial symptom onset to ZES diagnosis, presence of AST, diarrhea, abdominal pain, history of ulcers, surgery for ulcer-related complications, delay between symptom onset and surgery, FSG levels at diagnosis in pg/ml, results of SST and gastric acid output measurement), and preoperative imaging assessments (selective angiography, EUS, CT, MRI, Somatostatin Receptor Scintigraphy OctreoScan®, 18-Fluorodeoxyglucose or DOTATOC-(68Ga) PET / Computed Tomography PET/CT) were extracted from the database.

All surgeries were performed by a dedicated endocrine surgery team from an expert center of the ENDOCAN-RENATEN French Network, following a standardized protocol. The procedure included systematic abdominal exploration via open or minimally invasive approach using laparoscopy or robotic-assisted laparoscopy, liver and pancreatic intraoperative ultrasound, intraoperative endoscopic transillumination, duodenotomy and full exposure of the gastrinoma triangle, through the Kocher maneuver (6).

Tumor resections were adapted to tumor location including excision of duodenal wall patches for duodenal lesions, gastric or pancreatic resection including enucleation for pancreatic gastrinomas, and lymphadenectomy of the gastrinoma triangle. This triangle is anatomically defined by the junction of the cystic and common bile ducts superiorly, the junction of the pancreatic neck and body medially, and the second and third portions of the duodenum laterally. Lymphadenectomy involved removal of regional lymph nodes along the common bile duct, within the hepatoduodenal

ligament, around the pancreatic head and uncinate process, and near the duodenal wall adjacent to the superior mesenteric vessels (9).

Surgical characteristics (duration of surgery, surgical resections, lymph node dissection, cholecystectomy, intraoperative FSG level normalization, and hospital stay), histological characteristics (exact localization of primary tumor, lymph node metastasis and liver metastasis localization, pathological analysis outcome) were extracted from the database. Primary lymph node tumor was defined as a tumor confined to one or more resected lymph nodes within the “gastrinoma triangle”, with no evidence of extra nodal disease on preoperative imaging or intraoperative examination with normalization of gastrin levels associated with disease-free for 12 consecutive month follow-up post-resection as defined earlier (26).

Intraoperative gastrin sampling was performed at three principal time points: before tumor resection (T0), 20 minutes after tumor resection (T1), and 4 minutes after intravenous administration of secretin (T2). When performed, a secretin stimulation test was used to further assess the diagnosis. Additional samples could be obtained at the end of the procedure.

Biochemical intraoperative normalization of FSG was defined as normalization of FSG at T1 or at the end of the procedure. Biochemical intraoperative normalization of SST was defined as normalization of FSG at T1 associated with the absence of a gastrin increase at T2.

FSG samples were collected and analyzed by the Biochemistry Laboratory of Lille University Hospital, using validated assay methods. Before 2005, gastrin measurements were performed at the Nuclear Medicine Laboratory using radioimmunoassay, although the exact technique used during that period could not be retrospectively confirmed. From May 2005 to June 2022, measurements were

performed by radioimmunoassay (GASK-PR, Cisbio Bioassays, Codolet, France ; reference range < 120 pg/ml). From June 30, 2022 to March 9, 2023, measurements were performed by radioimmunoassay (Gastrin-RIA, ref. KIPEMD302, DiaSource, Louvain-la-Neuve, Belgium ; reference range 12-54 pmol/L), and from March 9, 2023 onwards, by radioimmunoassay (Gastrin-RIA, ref. MD302RUO, DiaSource ; reference ranges 12-54 pmol/L). Intraoperative gastrin measurements were occasionally performed using a chemiluminescent enzyme-labeled immunometric assay (Immulite 2000 Gastrin, ref. L2KGA2, Siemens Healthcare Diagnostics, Llanberis, United Kingdom; reference range <115 pg/ml).

Postoperative complications were recorded and classified according to the Clavien-Dindo grading system (27).

After the first postoperative month visit, follow-up, including clinical evaluation, FSG values and imaging results, was not standardized and was organized on a case-by-case basis depending on patient status (e.g., remission, recurrence). Data were collected either by the surgical team or by referring gastroenterologists and endocrinologists.

*Exposure and covariates*

The exposure of interest was **postoperative normalization of FSG** defined as a fasting serum gastrin level ≤ 120 pg/mL within the first postoperative month, following curative-intent surgery defined as the resection of all known primary and metastatic lesions, identified either preoperatively or intraoperatively, in addition to lymphadenectomy of the gastrinoma triangle.

By study design, patients with known residual tumor at the end of surgery procedures, i.e., those who underwent incomplete resection, were systematically classified as not achieving early postoperative normalization.

*Outcomes*

The primary outcome was the 20-year overall survival (OS). This information was primarily collected during postoperative follow-up consultations. For patients lost to follow-up, vital status was obtained through the French National Institute of Statistics and Economic Studies (INSEE) death registry, a national, official, and regularly updated database that records all deaths occurring in France and is commonly used for long-term survival assessment in French clinical cohorts (28).

Secondary outcomes included early postoperative complications, classified according to the Clavien-Dindo grading system (27) the total length of hospital stay, and the identification of predictive factors associated with early postoperative normalization of FSG levels.

*Statistical analysis*

Descriptive statistics were used to characterize the study population. Categorical variables were presented as frequencies and percentages, and continuous variables as means with standard deviations or medians with interquartile ranges, depending on the distribution assessed using histograms and the Shapiro–Wilk test.

Comparisons between patients with sporadic gastrinomas and those with multiple MEN1-associated gastrinomas were performed using chi-square or Fisher's exact test for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables, as appropriate.

Overall survival was estimated using Kaplan–Meier survival curves. Patients were further stratified according to whether they achieved or not postoperative normalization of fasting serum gastrin. Survival between these two groups was compared using Kaplan–Meier analysis with log-rank testing. The association was assessed using a Cox proportional hazards model, with adjustment for patient age at surgery and clinical status (sporadic versus MEN1-associated ZES), two confounding factors known to have an impact on overall survival.

Sensitivity analyses were conducted within sporadic and MEN1 subgroups to explore differences in survival patterns.

To identify predictive factors associated with early postoperative normalization of FSG, univariate logistic regression analyses were first conducted. Continuous variables that did not meet the log-linearity assumption—specifically age and preoperative FSG levels—were dichotomized using cut-off values close to their respective medians. Model assumptions, including multicollinearity, were tested prior to final inclusion.

All statistical analyses were performed using SAS University Edition (SAS Institute Inc., Cary, NC, USA). Graphs and survival curves were generated with GraphPad Prism (GraphPad Software, La Jolla, CA, USA). A two-sided p-value $< 0.05$ was considered statistically significant.

*Ethical Considerations*

This study was conducted in accordance with French data protection's regulations and approved by the National Commission for Informatics and Liberties (CNIL). No external funding was received.

The study complied with the standard operating procedures in place, in accordance with the European Data Protection Directive (95/46/EC) and, upon its entry into force, Regulation (EU) 2016/679 (also referred to as the General Data Protection Regulation) and French CNIL framework n° MR004 regarding the processing of personal data in clinical studies. The study report followed the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

## Results

*Baseline characteristics and follow-up*

One hundred and twelve patients with a clinical and/or biochemical, and/or imaging diagnosis of gastrinoma underwent curative-intent surgery in our institution between January 1985 and November 2024. Seventeen patients were excluded from the present analysis: fourteen patients for lack of pathological confirmation of gastrinoma (including 11 missing pathology reports and 3 negative gastrin IHC), one due to missing FSG assessment during the first postoperative month and two for uninterpretable postoperative FSG (atrophic gastritis or persistently normal preoperative FSG values). A total of 95 patients were enrolled in the present analysis (Figure 1).

Median follow-up was 12.1 (IQR 3.7-20.9) years. Thirty-two deaths occurred during follow-up, with the cause of death unknown in most cases. Vital status was available for all patients, with no missing data.

The median age at diagnosis was 55 (IQR 44-64) years, and 44 (46%) patients were female. Median body mass index (BMI) was 26 (IQR 22-29) kg/m² (Table 1).

MEN1 syndrome was diagnosed in 22 (23%) patients, with a genetically confirmed mutation in 16 (73%) of them. Seventy-two (77%) patients reported diarrhea and 51 (59%) had abdominal pain. A history of peptic ulcer disease was recorded in 71 (76%) patients. Among them, 22 (23%) had previously undergone surgery for ulcer-related complications prior to curative-intent gastrinoma resection.

The median diagnostic delay was 1.9 (IQR 0.6-5.9) years. Median preoperative FSG was 761 (IQR 306-1145) pg/mL. Distribution of preoperative serum gastrin levels at baseline is reported in supplemental Figure 1. SST and gastric acid output measurement were performed in 44 (46%) and 26 (27%) patients, respectively.

MEN 1 patients were significantly younger at diagnosis (44 years; IQR 38-60) compared to sporadic patients (56 years; IQR 48-64) (p = 0.052).

Time from symptoms and surgery was longer in MEN 1 patients (18.5 years; IQR 10.7-39.1) years compared to sporadic patients (8.7 years; IQR 5-13.5) (p= 0.037).

At the time of diagnosis, 93 (98%) patients presented with symptoms of ZES,

Diarrhea was significantly more frequent in sporadic patients (n = 59; 82%) compared to MEN 1 patients (n = 13; 59%) (p = 0.030).

87 (92%) had a biochemical diagnosis of ZES. 92 (97%) of the patients had positive diagnosis with localization of gastrinomas and/or metastasis on preoperative imaging.

All 95 patients underwent preoperative imaging, and their characteristics are summarized in Table 2.

The distribution across the three eras was as follows: 12 (13%), 64 (67%), 19 (20%) of the patients in Era 1, Era 2, and Era 3 respectively.

Selective angiography was performed in 11 (12%) patients, with a declining trend over time. Among these, 6 (55%) of the patients had positive diagnosis with localization of gastrinomas and/or metastasis (detection rates of gastrinomas on preoperative imaging are reported in Table 2)

EUS was performed in 81 (85%) of the patients with a positive detection of disease in 76 (94%).

CT was the most commonly used modality, performed in 89 (94%) patients, with a positive detection of the lesions increasing from 6 (60%) in era 1 to 42 (68%) and 15 (88%) in era 2 and 3 respectively, showing consistent utilization across all eras.

Regarding functional imaging, OctreoScan® scintigraphy was conducted in 65 (68%) patients, with positive detection of the lesion in 56 (86%).

Since its implementation in 2018, 68Ga-DOTATOC PET/CT has been routinely performed, with consistent diagnostic accuracy for detecting gastrinomas and/or metastases in all nineteen patients examined.

*Surgical characteristics detailed in Table 3*

Surgical procedures were performed in all 95 patients. The median operative time was 330 (IQR 240-390) minutes. Open surgery was the predominant approach, with 58 (63%) patients undergoing subcostal laparotomy, 29 (32%) midline laparotomy, and 5 (5%) minimally invasive surgery.

A duodenotomy was performed in 76 (81%) patients, and duodenal wall patches were carried out in 66 (69%) patients. Pancreatic resection was achieved in 23 (24%) patients, including 18 (19%) distal pancreatectomies, 5 (5%) enucleations, and 2 (2%) pancreaticoduodenectomies.

Lymph node dissection was performed in 77 (81%) patients with atypical liver resections for suspected metastases conducted in 13 (14%) patients.

Intraoperative serum gastrin level normalization was achieved in 34 (43%) patients.

Pancreatic resections were significantly more common in MEN1 patients (n = 11; 50%) compared to sporadic patients (n = 12; 16%) (p = 0.001), particularly distal pancreatectomy (50% compared to 10%; p = 0.022).

Lymph node dissection was significantly more frequent in sporadic patients (n = 63; 86%) compared to MEN1 patients (n = 14; 64%) (p = 0.017), while atypical liver resections were significantly more common in MEN1 patients (27% compared to 10%; p = 0.034).

Following surgery, a total of 69 (73%) patients achieved normalization of FSG in the first postoperative month. Median postoperative FSG was 76 (IQR 51-125) pg/mL.

*Tumor Histological Characteristics*

A primary tumor was identified in 69 (73%) of the 95 patients. Among these 69 patients, 57 (83%) had a duodenal primary tumor, 9 (13%) had a pancreatic primary tumor, 2 (3%) had a gastric primary tumor, and 1 (1%) had a gallbladder primary tumor (Figure 2).

Lymph node metastases were confirmed in 65 (71%) patients, while liver metastases were confirmed in 9 (9%) patients. At the time of data extraction, primary lymph node gastrinomas were observed in 12 (13%) patients.

Detailed pathological characteristics are shown in Table 4.

*Primary outcome*

Overall survival (OS) rate in the whole cohort was 82 % (95% CI 71-89) at 10 and 49 % (95% CI 36-61) at 20 years (KM estimates) (Figure 3A).

OS was significantly improved in patients who achieved normalization of FSG during the first postoperative month compared to those who did not achieve (Figure 3B) with an overall survival rate of 89 % (95% CI 77-95) compared to 60 % (95% CI 34-78) at the 10-year follow-up and 59% (95% CI 44-72) compared to 17% (95% CI 3-42) at the 20-year follow-up.

Normalization of FSG within the first postoperative month was significantly associated with improved overall survival, with an adjusted hazard ratio of 0.30 (95%

CI, 0.14-0.63; p = 0.0016). This association was independent from patient age at the time of surgery and whether the disease was sporadic or MEN1-associated.

Factors associated with early postoperative normalization of FSG within the first postoperative month were assessed using univariate logistic regression analysis. The corresponding forest plot is presented in Figure 4.

In univariate analysis, the presence of MEN 1 syndrome (OR 0.34; 95% CI, 0.12-0.92; p = 0.034) and the performance of a concomitant liver resection during surgery (OR 0.18; 95% CI, 0.05-0.60; p = 0.006) were both associated with a lower rate of FSG normalization within the first postoperative month. In contrast, baseline diarrhea (OR 3.17; 95% CI, 1.15-8.73; p = 0.026) was linked to a higher likelihood of postoperative FSG normalization.

A favorable, yet non-significant, trend was likewise observed for lymph-node dissection (OR = 1.94; 95% CI 0.66-5.72; p = 0.228) and for the presence of nodal metastases (OR = 1.96; 95% CI 0.74-5.18; p = 0.174).

*Secondary outcomes (Table 5)*

Postoperative complications occurred in 43 of the 95 patients (46%). Surgical complications were reported in 25 patients (27%) and included intra-abdominal infections (n = 8), duodenal fistulas (n = 4), pancreatic fistulas (n = 3), biliary fistulas (n = 2), intestinal occlusion (n = 2), hemorrhage (n = 2), stenosis requiring surgical intervention (n = 1), and other surgical events (n = 7).

Medical complications occurred in 22 patients (23%) and consisted of pulmonary embolism (n = 3), pneumonia (n = 1), and other medical complications (n = 18), including bacteremia or unexplained fever (n = 8), gastroparesis or diarrhea (n = 5), acute kidney injury or acute urinary retention (n = 2), blood transfusion in the absence of postoperative bleeding (n = 2), and confusion (n = 1).

Among patients with postoperative complication severity, graded according to the Clavien-Dindo classification, was mild (Grade ≤ 2) in 92 patients (98%) and severe (Grade 3) in 2 patients (2%). No Grade 4 or 5 complications were reported.

No significant differences were observed among patients with sporadic disease and those with MEN1-associated gastrinomas, including in terms of disease severity.

## Discussion:

In this retrospective cohort study, we investigated the association between postoperative normalization of FSG and 20-year overall survival in patients with ZES-related gastrinomas who benefited from curative intent surgery in Lille. Ten- and 20-year survival rates were 82 % (95% CI 71-89) and 49 % (95% CI 36-61). FSG normalization within the first postoperative month was achieved in 69 (73%) of 95 patients and was associated with improved survival: 89% (95% CI, 77-95) and 59% (95% CI, 44-72) at 10 and 20 years in patients who achieved postoperative FSG normalization, compared to 60% (95% CI, 34-78) and 17% (95% CI, 3-42) in patients who did not.

This association was independent from age or MEN1 status (adjusted HR = 0.30; 95% CI, 0.14-0.63; $p$ = 0.0016).

This study presents several strengths. First, this study benefits from a relatively large single-center cohort of ZES patients with histologically confirmed gastrinomas, which helps reduce the limitations associated with purely biochemical diagnoses. Second, all surgical procedures were performed by the same experienced endocrine surgery team following a consistent and standardized protocol, contributing to the homogeneity of care. Third, postoperative PPI therapy was systematically administered. Given that PPIs can elevate gastrin levels, the observation of early FSG normalization under these conditions further supports its potential relevance.

This study has limitations. First, its retrospective design and the absence of a controlled group may introduce selection and information bias. Diagnostic and therapeutic strategies evolved over time, leading to temporal heterogeneity. Second, gastrin assays and thresholds varied across the inclusion period, which may have affected interpretation despite a consistent definition of FSG normalization. Recent studies have shown substantial inter-assay variability among commercial immunoassays, with some kits producing falsely low values in up to 80% of patients. Their reliability is limited when FSG levels are below 845 pg/mL, a common range in ZES (29). Moreover, FSG remains an indirect marker of tumor activity. Persistent elevation may occur despite complete resection, due to rebound hypergastrinemia or PPI effect. Conversely, normal levels may be observed despite microscopic or non-secreting residual disease.

One limitation of our study was the absence of an exact preoperative fasting serum gastrin level in 16 patients (17%). However, these patients were included based on medical records confirming elevated levels at diagnosis, and all had histologically confirmed Zollinger-Ellison syndrome–related gastrinomas. We also acknowledge that patients with metastatic disease were assigned to the non-normalization group by design, which may have introduced bias given their poorer prognosis. Finally, tumor grade was not evaluated due to substantial missing data and classification inconsistencies, and cause of death was unavailable in most cases.

However, gastrin is known to exert mitogenic effects through the activation of the cholecystokinin B receptor (CCK2R), which subsequently triggers several intracellular signaling pathways including the MAPK/ERK pathway, PI3K/Akt pathway, and β-catenin signaling, ultimately promoting cellular proliferation and tumor growth (30).

Several studies have reported associations between chronic hypergastrinemia and an increased risk of gastrointestinal (31,32) and extra-digestive (33,34) malignancies. In this context, sustained elevated gastrin levels may act as a trophic factor that promotes tumor growth or recurrence. Therefore, early postoperative normalization of fasting serum gastrin could contribute to improved survival by eliminating this proliferative stimulus, in addition to reflecting effective tumor clearance.

Postoperative surveillance in Zollinger-Ellison syndrome remains particularly challenging. Clinical symptoms may be masked by the ongoing use of proton pump inhibitors, and imaging, despite technological advances such as 68Ga-DOTATOC PET can fail to detect microscopic or functionally silent lesions (22,23). In this context, early biochemical normalization of fasting serum gastrin may represent a useful surrogate marker for complete tumor resection. Conversely, the absence of early normalization could justify a closer and more frequent follow-up, even in the absence of radiological evidence of recurrence.

In conclusion, our findings demonstrate a positive and independent association between postoperative normalization of fasting serum gastrin after curative-intent surgery for Zollinger–Ellison syndrome–related gastrinomas and the 20-year overall survival. Although limited by the retrospective design and variable assay methodologies, this simple biomarker holds promise as an accessible prognostic tool to assess surgical completeness and inform postoperative surveillance. Prospective validation in larger cohorts, using standardized gastrin assays and extended follow-up, will be essential to confirm its clinical utility and refine its role in guiding management of ZES.

## Figures and tables:

**Table 1:** Demographic and Clinical Characteristics of the Patients at Baseline

| | All patients (n=95) | Sporadic (n=73) | MEN 1 (n=22) | p-value | missing values |
|---|---|---|---|---|---|
| **Female sex, n(%)** | 44 (46) | 33 (45) | 11 (50) | 0.693 | 0 |
| **Age - years, median (IQR)** | 55 (44-64) | 56 (48-64) | 44(38-60) | 0.052 | 0 |
| **BMI - kg/m2, median (IQR)** | 26 (22-29) | 25 (22-29) | 27 (24-30) | 0.444 | 6 |
| **History** | | | | | |
| **Type 2 diabetes, n(%)** | 11 (12) | 7 (10) | 4 (18) | 0.270 | 0 |
| **Tobacco use, n(%)** | 49 (56) | 40 (55) | 9 (41) | 0.395 | 8 |
| **Diagnostic delay - yrs, median (IQR)** | 1.9 (0.6-5.9) | 1.9 (0.8-5.6) | 2 (0-6) | 0.999 | 3 |
| **Primary hyperparathyroidism, n(%)** | 17 (18) | 0 (0) | 17 (77) | **<0.0001** | 0 |
| **Parathyroidectomy history, n(%)** | 15 (16) | 0 (0) | 15 (71) | **<0.0001** | 1 |
| **Pituitary adenoma, n(%)** | 9 (9) | 0 (0) | 9 (41) | **<0.0001** | 0 |
| **Symptoms** | | | | | |
| **Diarrhea, n(%)** | 72 (77) | 59 (82) | 13 (59) | **0.037** | 1 |
| **Abdominal pain, n(%)** | 51 (59) | 42 (63) | 9 (45) | 0.159 | 8 |
| **Anti acid therapy, n(%)** | 87 (93) | 67 (93) | 20 (91) | 0.737 | 1 |
| **Ulcer history, n(%)** | 71 (76) | 58 (81) | 13 (62) | 0.077 | 2 |
| **Gastric, n(%)** | 32 (34) | 26 (36) | 6 (29) | 0.522 | |
| **Duodenal, n(%)** | 47 (51) | 39 (54) | 8 (38) | 0.195 | |
| **Jejunal, n(%)** | 11 (12) | 11 (15) | 0 (0) | 0.057 | |
| **Surgery for complicated ulcer, n(%)** | 22 (23) | 19 (26) | 3 (14) | 0.227 | 0 |
| **Delay between symptoms and surgery - yrs, median (IQR)** | 9.8 (5.3-19.1) | 8.7 (5-13.5) | 18.5 (10.7-39.1) | **0.037** | 0 |
| **Fasting serum gastrin level* - pg/mL, median (IQR)** | 761 (306-1145) | 793 (393-1115) | 601 (227-1270) | 0.820 | 13 |

**Table 2:** Imaging Characteristics of the Patients at Baseline

| | Era 1 * 1985 to 1991 | Era 2 ** 1991 to 2018 | Era 3 *** 2018 to 2024 | All patients (n=95) | missing values |
|---|---|---|---|---|---|
| **n (%)** | 12 (13) | 64 (67) | 19 (20) | 95 (100) | 0 |
| **Selective angiography** | 6 (50) | 5 (8) | 0 (0) | 11 (12) | |
| **Positive lesion detection, n(%)** | 4 (67) | 2 (40) | 0 (0) | 6 (55) | |
| **Endoscopic ultrasound** | 3 (25) | 60 (94) | 18 (95) | 81 (85) | |
| **Positive lesion detection, n(%)** | 2 (67) | 57 (95) | 17 (94) | 76 (94) | |
| **CT scan** | 10 (83) | 62 (97) | 17 (89) | 89 (94) | |
| **Positive lesion detection, n(%)** | 6 (60) | 42 (68) | 15 (88) | 63 (71) | |
| **MRI** | 4 (33) | 26 (41) | 17 (89) | 47 (49) | |
| **Positive lesion detection, n(%)** | 4 (100) | 16 (62) | 8 (47) | 28 (60) | |
| **SR Scintigraphy** | 0 (0) | 64 (100) | 1 (5) | 65 (68) | |
| **Positive lesion detection, n(%)** | 0 (0) | 55 (86) | 1 (100) | 56 (86) | |
| **18F-FDG PET** | 1 (8) | 5 (8) | 5 (26) | 11 (12) | |
| **Positive lesion detection, n(%)** | 1 (100) | 3 (60) | 1 (20) | 5 (45) | |
| **68Ga-DOTATOC PET** | 0 (0) | 0 (0) | 19 (100) | 19 (20) | |
| **Positive lesion detection, n(%)** | 0 (0) | 0 (0) | 19 (100) | 19 (100) | |

**Abbreviations**: CT scan = Contrast-enhanced computed tomography, MRI = Magnetic resonance imaging, SR = Somatostatin receptor, PET = Positron emission tomography.

**Table 3:** Surgery Characteristics

| | All patients (n=95) | Sporadic (n=73) | MEN 1 (n=22) | p-value | missing values |
|---|---|---|---|---|---|
| **Surgery duration - min, median (IQR)** | 330 (240-390) | 320 (240-380) | 360 (307-450) | 0.331 | 24 |
| **Surgical approach** | | | | **0.005** | 3 |
| **Subcostal laparotomy, n(%)** | 58 (63) | 48 (67) | 10 (50) | | |
| **Median laparotomy, n(%)** | 29 (32) | 23 (32) | 6 (30) | | |
| **Mini-Invasive, n(%)** | 5 (5) | 1 (1) | 4 (20) | | |
| **Duodenotomy, n(%)** | 76 (81) | 59 (82) | 17 (77) | 0.626 | 1 |
| **Duodenal wall patches, n(%)** | 66 (69) | 52 (71) | 14 (64) | 0.497 | 0 |
| **Gastric resection, n(%)** | 9 (9) | 9 (12) | 0 (0) | 0.084 | 0 |
| **Pancreatic resection, n(%)** | 23 (24) | 12 (16) | 11 (50) | **0.001** | 0 |
| **Enucleation, n(%)** | 5 (5) | 5 (7) | 0 (0) | **0.022** | |
| **Distal pancreatectomy, n(%)** | 18 (19) | 7 (10) | 11 (50) | **0.022** | |
| **Pancreaticoduodenectomy, n(%)** | 2 (2) | 2 (3) | 0 (0) | **0.022** | |
| **Lymph node dissection, n(%)** | 77 (81) | 63 (86) | 14 (64) | **0.017** | 0 |
| **Atypical liver resection - n(%)** | 13 (14) | 7 (10) | 6 (27) | **0.034** | 0 |
| **Cholecystectomy, n(%)** | 58 (62) | 46 (64) | 12 (55) | 0.433 | 1 |
| **Intraoperative serum gastrin level normalization, n(%)** | 34 (43) | 30 (46) | 4 (29) | 0.228 | 16 |
| **Hospital stay - days, median (IQR)** | 12 (9-19) | 12 (9-17) | 14 (8-26) | 0.982 | 3 |

IQR= Inter Quartile Range

**Table 4:** Histological Characteristics

| | All patients (n=95) | Sporadic (n=73) | MEN 1 (n=22) | p-value | missing values |
|---|---|---|---|---|---|
| **Primary tumor, n(%)** | 69 (73) | 51 (70) | 18 (82) | 0.270 | 0 |
| **Duodenal, n(%)** | 57 (60) | 41 (56) | 16 (73) | 0.165 | 0 |
| **Pancreatic, n(%)** | 9 (9) | 7 (10) | 2 (9) | 0.944 | 0 |
| **Stomach, n(%)** | 2 (2) | 2 (3) | 0 (0) | 0.433 | 0 |
| **Gallbladder, n(%)** | 1 (1) | 1 (1) | 0 (0) | 0.581 | 0 |
| **Lymph node metastasis, n(%)** | 65 (71) | 51 (72) | 14 (67) | 0.648 | 3 |
| **Liver metastasis, n(%)** | 9 (9) | 6 (8) | 3 (14) | 0.164 | 0 |
| **Primary lymph node localization*, n(%)** | 12 (13) | 11 (15) | 1 (5) | 0.187 | 1 |

*long-term cure after resection of only a lymph node gastrinoma

**Table 5:** Postoperative Characteristics

| | All patients (n=95) | Sporadic (n=73) | MEN 1 (n=22) | p-value | missing values |
|---|---|---|---|---|---|
| **Postoperative complications, n(%) of patients** | 43 (46) | 31 (43) | 12 (57) | 0.234 | 1 |
| **Surgical complications, n(%)** | 25 (27) | 17 (23) | 8 (36) | 0.176 | |
| **Intra-abdominal infection, n(%)** | 8 (9) | 3 (4) | 5 (23) | | |
| **Duodenal fistula, n(%)** | 4 (4) | 2 (3) | 2 (9) | | |
| **Pancreatic fistula, n(%)** | 3 (3) | 1 (1) | 2 (9) | | |
| **Biliary fistula, n(%)** | 2 (2) | 2 (3) | 0 (0) | | |
| **Occlusion, n(%)** | 2 (2) | 2 (3) | 0 (0) | | |
| **Evisceration, n(%)** | 0 (0) | 0 (0) | 0 (0) | | |
| **Stenosis requiring surgery, n(%)** | 1 (1) | 1 (1) | 0 (0) | | |
| **Hemorrhage, n(%)** | 2 (2) | 2 (3) | 0 (0) | | |
| **Others, n(%)** | 7 (7) | 6 (8) | 1 (4) | | |
| **Medical complications, n(%)** | 22 (23) | 16 (22) | 6 (27) | 0.924 | |
| **Pulmonary artery embolism, n(%)** | 3 (3) | 1 (1) | 2 (9) | | |
| **Pneumopathy, n(%)** | 1 (1) | 0 (0) | 1 (4) | | |
| **Others, n(%)** | 18 (19) | 15 (21) | 3 (14) | | |
| **Clavien-Dindo** | | | | 0.631 | 1 |
| **Grade ≤2, n(%)** | 92 (98) | 71 (97) | 21 (100) | | |
| **Grade = 3, n(%)** | 2 (2) | 2 (3) | 0 (0) | | |
| **Grade = 4, n(%)** | 0 (0) | 0 (0) | 0 (0) | 1 | |
| **Grade = 5, n(%)** | 0 (0) | 0 (0) | 0 (0) | 1 | |
| **Follow up – years, median (IQR)** | 12.1 (3.7-20.9) | 12.3 (5.3-21.6) | 10.2 (2.7-14.5) | 0.228 | 0 |

**Figure 1:** Flowchart of the study

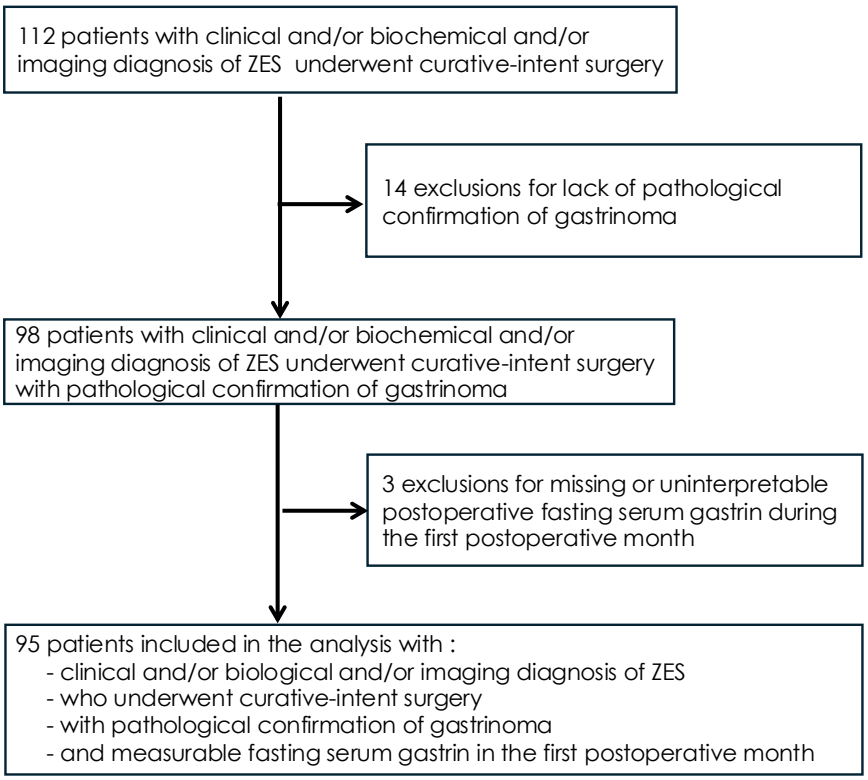
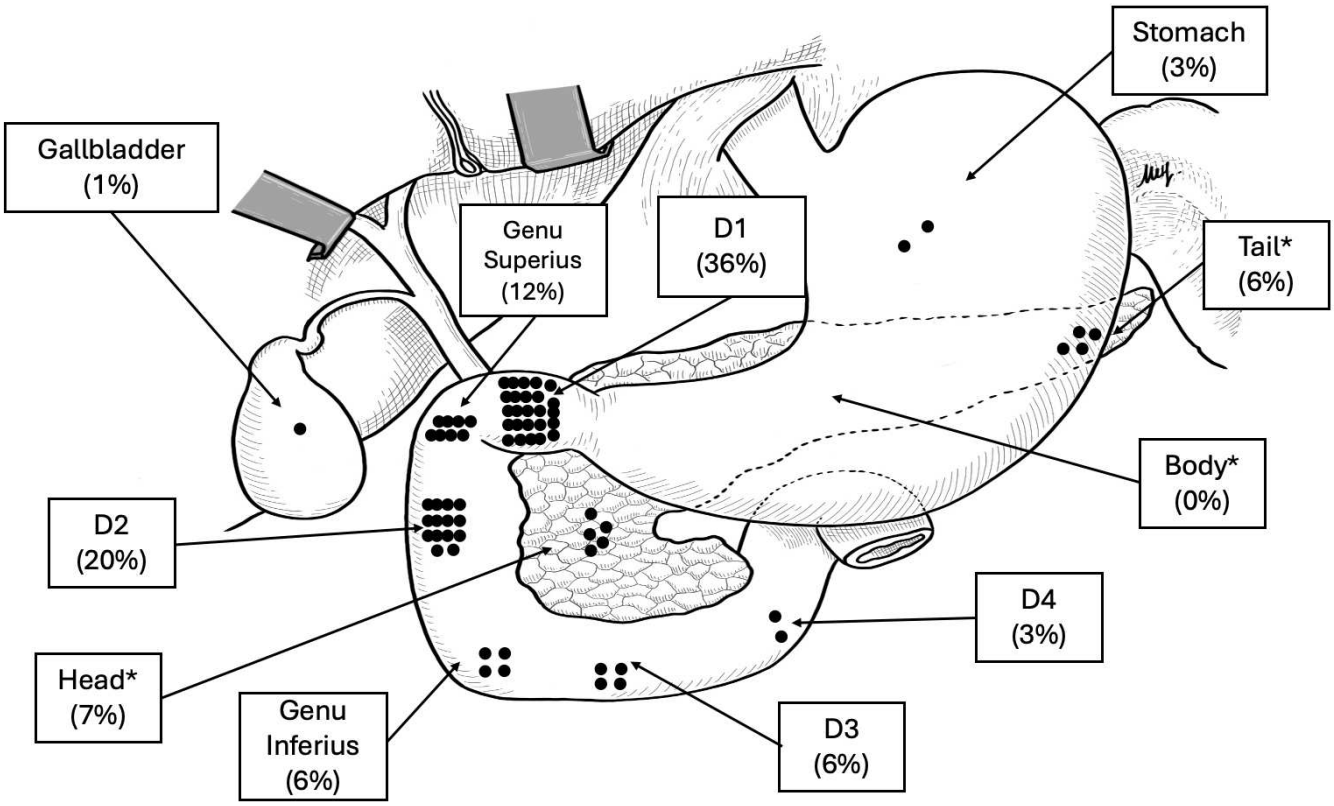
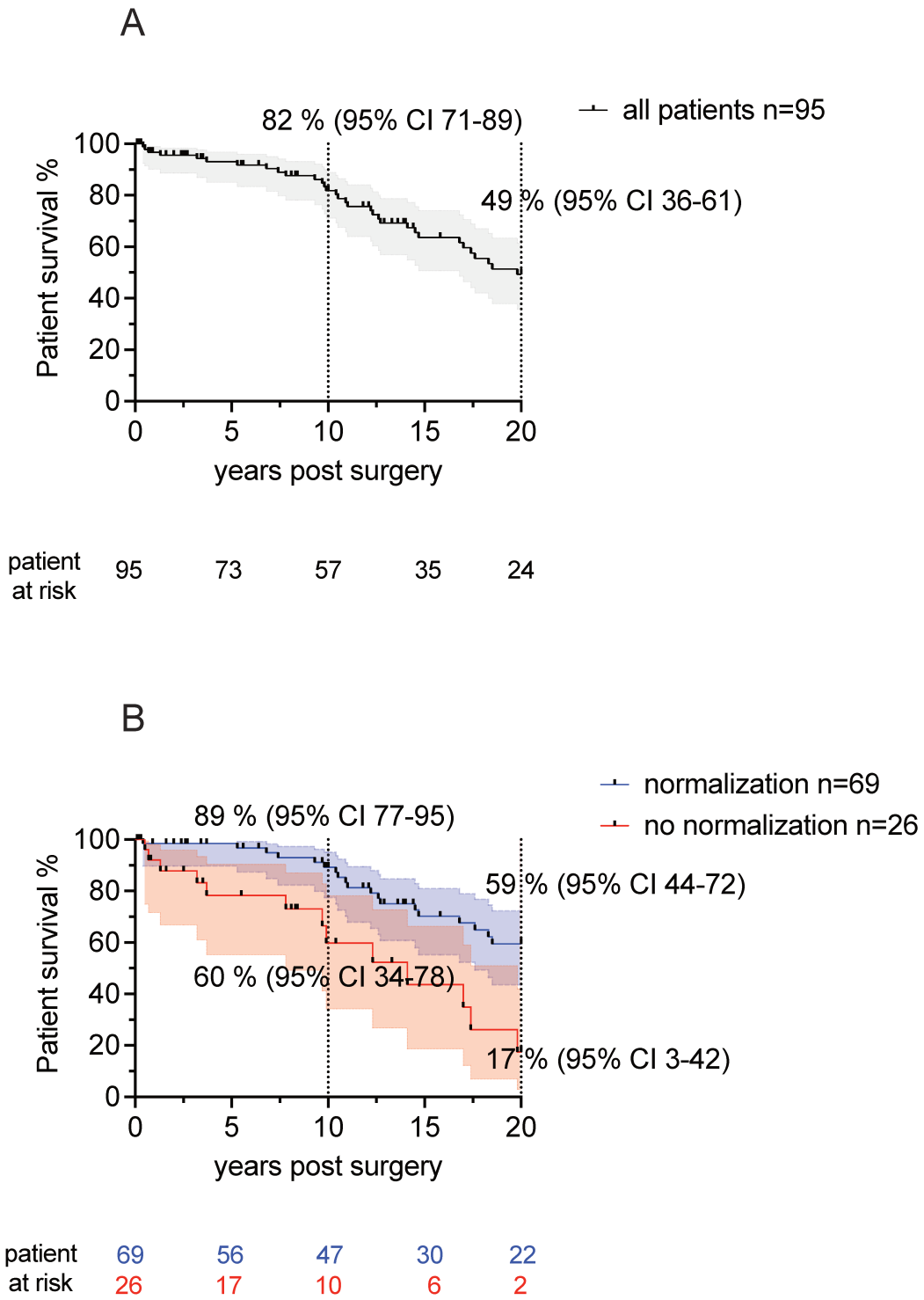


**Figure 2:** Anatomical distribution of primary tumors.



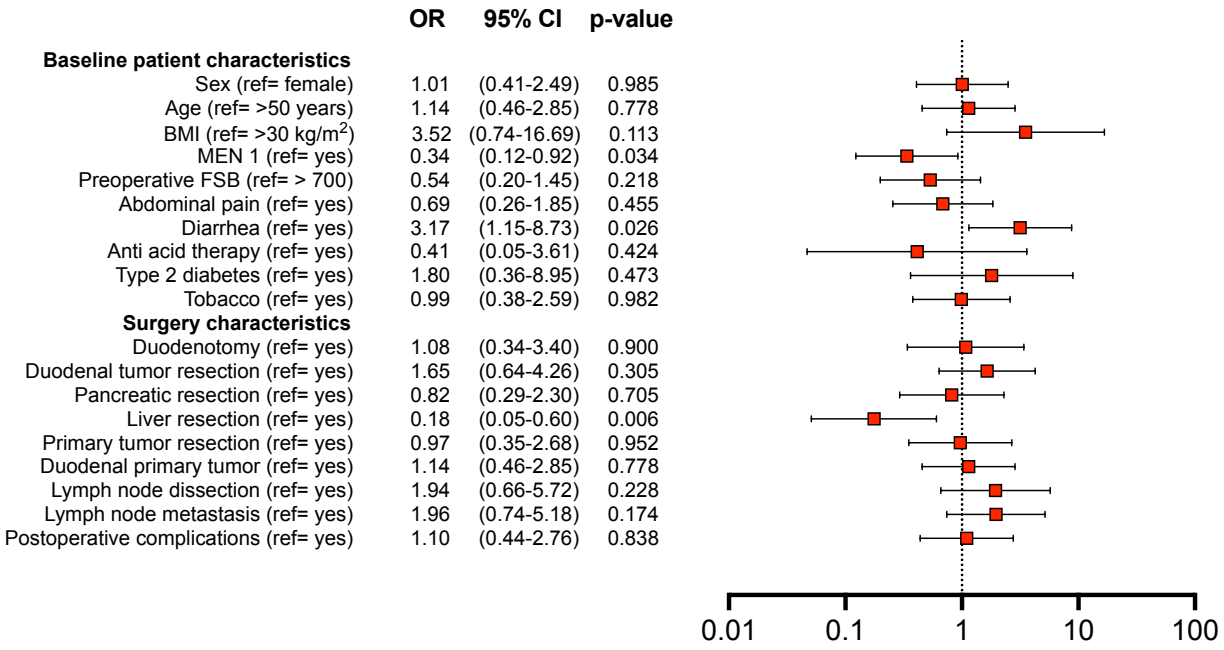

Anatomical distribution of primary tumors (n=69). Each black dot represents a primary tumor localization identified. D1-D4= first to fourth portions of the duodenum. * of the pancreas

**Figure 3:** Overall survival of the whole cohort and according to postoperative normalization of FSG status



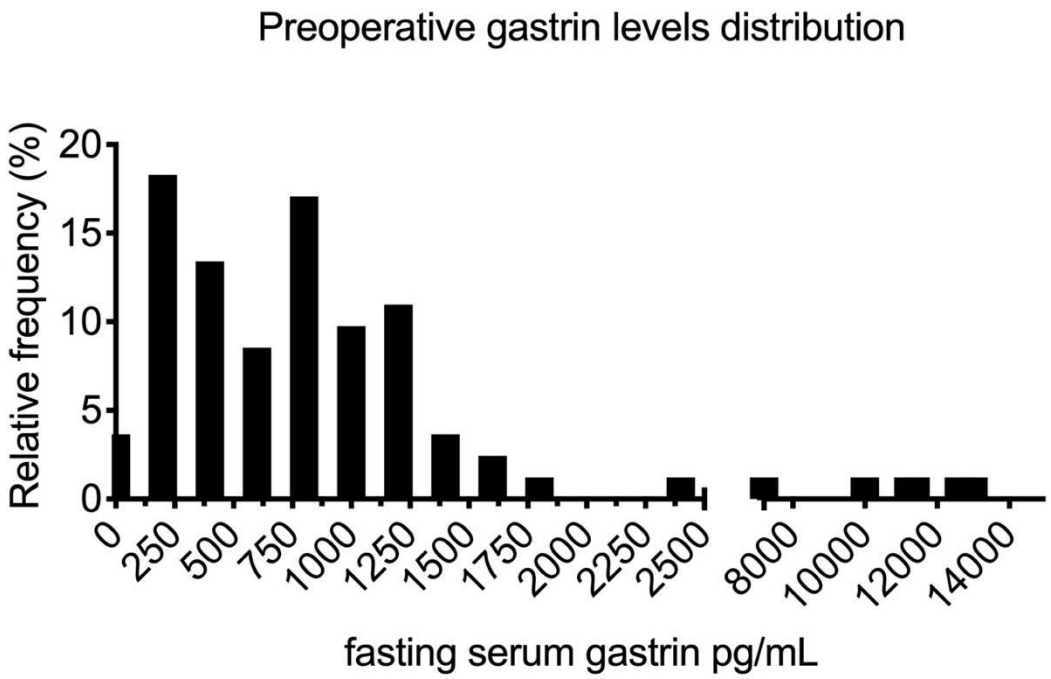
Kaplan-Meier overall survival curves for all 95 patients included in the study, stratified by postoperative fasting serum gastrin (FSG) normalization status. Early postoperative normalization was defined as FSG ≤ 120 pg/mL within 30 days post-surgery.

**Figure 4:** Univariate analysis of factors related to early postoperative biochemical normalization.




Forest plot illustrates the results of univariate logistic regression analysis for factors associated with normalization of FSG (defined as FSG ≤ 120 pg/mL within 30 days post-surgery). Variables included clinical, biological, imaging, and surgical parameters. Odds ratios (OR) with corresponding 95% confidence intervals and p-values are displayed for each variable on a log 10 scale to facilitate interpretation of effect sizes across multiple variables.

Supplemental Figure 1



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## Discussion Générale:

La prise en charge thérapeutique du SZE a connu des évolutions majeures au cours des dernières décennies. L'introduction des IPP dans les années 1980 a transformé la gestion symptomatique en offrant un meilleur contrôle de l'hypersécrétion acide et une nette amélioration de la qualité de vie des patients(16). Cependant, seule la résection chirurgicale reste potentiellement curative, en particulier dans les formes sporadiques(17).

L'imagerie a connu des avancées majeures avec la scintigraphie à la somatostatine (OctreoScan®), puis plus récemment avec le PET/CT au 68Ga-DOTATOC (11,12), permettant une détection plus précoce des lésions primaires et des métastases, y compris de très petite taille. Ces progrès ouvrent de nouvelles perspectives vers des approches de chirurgie mini-invasive, plus ciblées et moins délétères, notamment pour les tumeurs localisées duodénales ou pancréatiques. Toutefois, ces techniques restent actuellement réservées à des équipes hautement spécialisées, et la chirurgie standardisée par laparotomie avec curage du triangle du gastrinome demeure la référence.

Malgré ces progrès, plusieurs incertitudes subsistent. La définition diagnostique du SZE reste largement fondée sur des critères biologiques sujets à des difficultés d'application en pratique courante (18), et à des variations importantes selon les techniques de dosage (19). De plus, la stratégie chirurgicale dans le contexte du SZE associé à la NEM1 demeure débattu (20–22), en raison de la fréquence des lésions multiples souvent de faible agressivité.

Enfin, le rôle trophique et mitogène de la gastrine a été démontré dans la prolifération tumorale, en particulier dans les cancers colorectaux et gastriques (23), pancréatiques (24) et hépatocellulaires (25), ainsi que dans certaines tumeurs extra-digestives comme les cancers pulmonaires (26) et rénaux (27). La normalisation postopératoire de la gastrinémie pourrait ainsi refléter la suppression d'un potentiel stimulus tumoral, contribuant à améliorer le pronostic.

En conclusion, nos résultats mettent en évidence l'association positive entre la normalisation postopératoire de la gastrinémie à jeun après une chirurgie à visée curative pour un gastrinome lié au syndrome de Zollinger–Ellison, et la survie à 20 ans. Bien que cette observation soit limitée par la nature rétrospective de l'étude et la variabilité des méthodes de dosage, ce biomarqueur simple apparaît prometteur en tant qu'outil pronostique accessible pour évaluer l'exhaustivité de la résection chirurgicale et orienter la surveillance postopératoire. Une validation prospective sur de plus larges cohortes, avec des dosages de gastrine standardisés et un suivi prolongé, sera indispensable pour confirmer son utilité clinique et affiner son rôle dans la prise en charge du SZE.

**References (Introduction et Discussion générale)**


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**Titre de la thèse : Impact de la normalisation précoce de la gastrinémie postopératoire sur la survie à long terme après traitement chirurgical du gastrinome.**

**Thèse - Médecine - Lille 2025**

**Cadre de classement :** *Chirurgie viscérale*

**DES + FST/option :** *Chirurgie viscérale et digestive*

**Mots-clés :** Gastrinome, Néoplasies neuroendocriniennes, tumeurs neuroendocrines, syndrome de Zollinger-Ellison, gastrinémie.

**Objectif :** Le syndrome de Zollinger-Ellison (SZE) est une affection rare causée par une tumeur neuroendocrinienne fonctionnelle sécrétant de la gastrine (gastrinome), et entraînant une hypersécrétion d'acide gastrique ainsi que des ulcères gastroduodénaux récidivants. Bien que la chirurgie soit le seul traitement curatif, il n'existe toujours pas de marqueurs pronostiques postopératoires précoces fiables. Nous avons cherché à évaluer si la normalisation de la gastrinémie à jeun (GJ) au cours du premier mois postopératoire était associée à la survie globale des patients à 20 ans.

**Patients et méthodes :** Cette étude de cohorte rétrospective monocentrique a inclus tous les patients adultes ayant subi une chirurgie à visée curative pour un SZE au CHU de Lille entre 1985 et 2024, avec confirmation histologique et disposant d'une GJ, éligibles à l'analyse. Le facteur d'exposition de l'étude était la normalisation précoce de la GJ postopératoire, définie par un taux ≤120 pg/mL mesuré au cours du premier mois après l'intervention chirurgicale. Le critère de jugement principal était la survie globale à 20 ans (Kaplan-Meier).

**Résultats :** Parmi les 95 patients inclus dans l'analyse, l'âge médian était de 55 ans (IQR 44-64) ; 44 femmes (46 %), 69 (73 %) ont obtenu une normalisation de la GJ au cours du premier mois postopératoire. Le taux de survie globale pour l'ensemble de la cohorte était de 82 % (IC 95 % 71-89) à 10 ans et de 49 % (IC 95 % 36-61) à 20 ans. Le taux de survie globale était significativement meilleur chez les patients ayant normalisé leur GJ après l'intervention, avec des taux de survie à 10 ans et 20 ans de 89 % (IC 95 % 77-95) et 59 % (IC 95 % 44-72) contre 60 % (IC 95 % 34-78) et 17 % (IC 95 % 3-42) chez ceux n'ayant pas atteint la normalisation : Hazard Ratio ajusté 0,30 (IC 95 % ; 0,14-0,63 ; p = 0,0016). Cette association était indépendante de l'âge du patient au moment de la chirurgie et du caractère sporadique ou associé à une MEN1 de la maladie.

**Conclusion :** La normalisation de la gastrinémie dans le premier mois postopératoire après chirurgie curative pour SZE est associée à une meilleure survie globale. Elle pourrait représenter un marqueur pronostique pertinent, à valider dans des études prospectives.

**Composition du Jury :**

**Président : Monsieur le Professeur François PATTOU**

**Assesseurs : Monsieur le Professeur Pascal HAMMEL, Monsieur le Professeur Robert CAIAZZO, Madame le Docteur Christine DO CAO, Monsieur le Docteur Julien BRANCHE**

**Directeur de thèse : Monsieur le Docteur Mikaël CHETBOUN**