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Value of Surgery In Patients With Negative Imaging And Sporadic Zollinger-Ellison Syndrome (ZES)

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Abstract

Objectives—To address the value of surgery in sporadic Zollinger-Ellison syndrome (ZES) patients with negative imaging studies.

Background—Medical control of acid hypersecretion in patients with sporadic Zollinger-Ellison syndrome (ZES) is highly effective. This has led to these patients frequently not sent to surgery, especially if preoperative imaging studies are negative, due in large part because almost no data exists on the success of surgery in this group.

Methods—58 prospectively studied sporadic ZES patients (17% of total studied) had negative imaging studies and their surgical outcome was compared to 117 patients with positive imaging results.

Results—35 patients had negative imaging in the pre-somatostatin receptor scintigraphy era (SRS) and 23 in the post-SRS era. The image negative patients had long disease histories prior to surgery (mean±SEM, from onset=7.9±1[range −0.25-35 yrs]) and 25% were followed ≥2yrs from diagnosis. At surgery, gastrinoma was found in 57/58 patients (98%). Tumors were small (mean=0.8cm, 60% < 1 cm). The most common primary sites were: duodenal 64%, pancreatic 17%, and lymph node (LN)(10%). 50% had a primary only, 41% primary + LN, and 7% had liver metastases. 35/58(60%) were cured immediately postoperatively and at last follow-up [mean-9.4yrs, range 0.2-22yrs], 27 patients (46%) remained cured. During follow-up 3 patients died, each was found to have liver metastases at surgery. In comparison to the image positive patients, those with negative imaging had lower preop fasting gastrin levels; a longer delay prior to surgery; more frequently had a small duodenal tumors; less frequently had a pancreatic tumor, multiple tumors or developed a new lesion postoperatively and had a longer survival.

Conclusions—Imaging negative sporadic ZES patients are not rare even in the post-SRS period. An experienced surgeon can find gastrinoma in almost every patient (98%) and nearly one-half (46%) are cured, a rate similar to imaging positive tumor patients. Because liver metastases were

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found in 7%, which may have been caused by a long delay in surgery and all the disease-related deaths occurred in this group, surgery should be routinely undertaken early in ZES patients despite negative imaging studies.

Keywords

Gastrinoma; imaging negative; surgery; outcome

Introduction

Medical therapy has become increasingly effective in the control of gastric acid hypersecretion in Zollinger-Ellison syndrome patients to the present, where acid can now be controlled in almost every patient both acutely and long-term, thus total gastrectomy is rarely needed [1]. This approach became possible first with the development and widespread use of the histamine receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine) in the late 1970-1980s and later the development of the long-acting proton pump inhibitors (omeprazole, lansoprazole, rabeprezole, esomeprazole, pantoprazole), which allowed once or twice a day dosing in most patients [123]. The success of medical therapy coupled with the fact that gastrinomas are frequently not localized preoperatively [456] and that in many patients with ZES the gastrinomas show indolent behavior [7] has led to a number of groups recommending that surgical exploration not be routinely performed or that it only be performed in patients where the preoperative imaging localizes a likely primary tumor [89101112131415]. Recent studies show that the use of PPIs is not only delaying the diagnosis and but also delays the time patients are sent to surgery, so that patients have more advanced disease [316].

This latter recommendation has partially developed because of the lack of data on the efficacy of surgery in imaging negative patients with ZES. Some studies [1718], containing primarily sporadic ZES patients with positive imaging results, have shown that surgical removal of the gastrinoma can increase survival by decreasing disease-related deaths, resulting in a decrease in the postoperative development of liver metastases, which are the major prognosticators of survival in ZES [18,19]. However, no studies have specifically dealt with effectiveness of surgery in the imaging negative groups of patients with sporadic ZES.

In the present study we have attempted to address this issue by comparing from our prospective study of 229 ZES patients, the surgical results in 58 sporadic ZES patients with preoperative negative imaging (35 in the pre-Somatostatin receptor scintigraphy era (SRS), and 23 in the post SRS era) to the results of 117 patients with positive imaging operated over the same time period.

Methods

Two prospective databases of patients who underwent surgery to remove gastrinoma and cure ZES were reviewed [5,19]. In one, surgery was done at Stanford University hospital (SUH) since 1996 and, in the other, at the National Institutes of Health (NIH) since 1981. The main outcome measures were overall survival, disease-related survival, and time to development of any recurrence and liver metastases.

The diagnosis of ZES was based on measurement of an elevated fasting serum level of gastrin (> 100 pg/ml), an elevated basal acid output (>10 mEq/h), and the results of secretin and calcium provocative tests [2021]. Basal and maximal acid output (BAO, MAO) was determined for each patient using methods described previously. Briefly, each patient had an elevated fasting serum level of gastrin and a concomitant elevated basal acid output. Most

patients also had an abnormal secretin test (>120 pg/ml increment in gastrin following iv 2U/kg secretin) [21]. These studies confirmed the diagnosis of Zollinger-Ellison syndrome for each patient. After confirming the diagnosis, patients underwent detailed imaging studies (thin slice CT scan with intravenous contrast, MRI with gadolinium, ultrasound [22], and since 1994 each underwent somatostatin receptor scintigraphy (using [^{111}In-DTPA-DPhe^{1}]-octreotide (6 mCi) with whole body, planar, and SPECT views)[4,2324,25, 22,] and in selected cases abdominal angiography to determine precise tumor localization and operability as described previously. In some patients if SRS and conventional localization was equivocal, either selective venous sampling for gastrin gradients basally [26] or after secretin injection and hepatic venous sampling [27] was used to regionally localize the tumor [28]. Patients were invited to undergo surgery to remove the tumor if they had no co-morbid medical condition markedly limiting life expectancy, had imaging evidence of either operable localized tumor or no tumor identified [292530]. In this particular study patients with either preoperative imaging evidence of liver metastases or family history and biochemical evidence of MEN-1 were excluded and only patients with sporadic ZES with either imaging localized or imaging negative gastrinomas were included.

A detailed past history of disease was taken at first admission and past medical/surgical procedures as described previously [6]. Time from onset of symptoms to exploration was determined for all patients. The time of diagnosis of ZES was the time the diagnosis was first established by appropriate laboratory studies, when a physician established the diagnosis based on clinical presentation or when the histological diagnosis was established [6].

The operative techniques have been described previously [30315,18]. The pancreas and duodenum were widely exposed by dividing the inferior border of the body and tail of the pancreas and performing an extended Kocher maneuver during which the right colon and hepatic flexure were mobilized away from the pancreas and duodenum. Intraoperative ultrasound of the pancreas and duodenum was systematically performed on all patients [32]. The duodenum was routinely opened longitudinally and closed transversely in all patients unless a gastrinoma was located in the body or tail of the pancreas [5]. A detailed inspection for peripancreatic, periduodenal, or portohepatic lymph nodes was carried out, and these were routinely removed. Tumors in the pancreatic head were enucleated. Tumors in the pancreatic body and tail were resected with a distal pancreatectomy splenectomy. If a large pancreatic head tumor was present and could not be enucleated, a pancreaticoduodenectomy was performed. If liver metastases were present, they were biopsied and excised by either wedge resection or anatomical resection. Postoperatively, patients underwent evaluation for disease-free status immediately after surgery (i.e., 2 weeks post-resection), within 3 to 6 months post-resection, and then yearly [33625,34]. Yearly evaluations included conventional imaging studies (CT, ultrasound, MRI, and angiography, if necessary); somatostatin receptor scintigraphy since 1994; assessment of fasting serum level of gastrin, secretin stimulated gastrin level and acid output. Complete disease-free status (or cure) is defined as normal fasting serum levels of gastrin, negative secretin test and no evidence of tumor on postoperative imaging studies including CT and SRS [3056,34]. A recurrence post-resection was defined as occurring in a patient who was initially disease-free, but then lost disease-free status on follow-up evaluation by developing positive imaging studies or recurrent elevated fasting serum gastrin levels [25].

All continuous variables were reported as mean ± standard error of the mean. Survival analysis was done using the Kaplan–Meier method and two-group comparisons using log-rank tests. Proportions are compared statistically by Fisher exact test. Statistical analyses were performed by means of the SAS statistical software package and significance was defined as two-tailed P value less than 0.05.

Results

339 patients with ZES were identified which includes 110 patients with MEN-1 and 229 sporadic patients. This analysis excludes patients with MEN-1 such that of the 229 sporadic ZES patients 58 had negative preoperative imaging and those are compared to 117 with positive imaging who underwent the same operation. Of the imaging negative cohort 35 patients were from the pre-SRS era and had negative conventional imaging studies (CT, MRI, ultrasound) and angiography, whereas 23 were from the post-SRS period [23] and had both SRS as well as the imaging studies described for the pre-SRS group. Of the 58 image negative patients, 33 (57%) were male, the mean age was 42.6 years and 48.8 at onset or diagnosis of ZES, the main presenting symptom was upper abdominal pain and none of these variables was different from the imaging positive cohort (Table 1). However, the proportion with prior abdominal surgery (10%) and acid-related surgery (3.4%) was significantly lower in the imaging negative group compared to the imaging positive group 44% and 21%, respectively (Table 1). This was not true for hiatal hernia surgery that was higher proportionally in the imaging negative group, 8.6% vs 0.8%. The fasting serum gastrin level was significantly lower for the imaging negative group, but the delta secretin and the BAO were not different (Table 1).

57 of 58 (98%) of the imaging negative patients had gastrinoma excised at surgical exploration, and although there was a trend (p=0.059), this was not different from the imaging positive patients of whom 90.5% had gastrinoma excised (Table 2). Of the imaging negative patients, significantly more tumors were found in the duodenum 64% compared to 37%, p=0.0008; further, significantly less tumors were found in the pancreas 15.5% compared to 30%, p=0.039. In the imaging negative group, there were no truly extra-pancreatic, extra-duodenal tumors compared to 10.2% in the imaging positive group p= 0.008 (Table 2). The exact distribution of gastrinomas found at surgery in the preoperative image negative patients is shown in Figure 1. Most are found in the first and second portion of the duodenum (61%), while another important group (29%) is lymph nodes that are found in the area of the pancreatic head. There is a uniform distribution of pancreatic gastrinomas throughout the pancreas. The size of the imaging negative tumors is smaller than the ones that are imaged preoperatively (1 cm vs. 1.9cm). A significantly higher proportion of these tumors are less than 1 cm (62% compared to 20.5%) and a significantly lesser proportion is greater than 3 cm (1.7% vs. 18%) (Table 2). Despite the fact that the imaging was negative, a similar proportion had biopsy proven liver metastases (6.8%) as the imaging positive patients (7.7%). The surgical procedures and complications (34% both groups) were similar in the imaging negative and imaging positive cohort (Table 3). A higher proportion of imaging negative patients waited over 10 years from onset of ZES to surgery (38% vs 25%, p=0.036). The procedures performed were similar in the two groups except the imaging negative patients had a greater proportion of proximal pancreaticoduodenectomies 6.8% vs. 0.8%, p=0.024). The operative deaths were the same with no deaths in the imaging negative group and 1 (0.8%) in the imaging positive group.

The mean postoperative follow-up is approximately 10 years and it is similar between the two groups (Table 4). The proportion of patients who are alive at last follow-up and had conversely disease-related deaths showed a trend to superiority in the image negative groups (p=0.062), but it did not reach statistical significance. The proportion of patients who are disease-free is 48% in the imaging negative group and is not different from the 35% in the imaging positive group. There was no difference in the proportion of patients who developed liver metastases after surgery, nor the time to development of liver disease; however, the number of patients developing new imageable lesions following surgery was only 21% in the imaging negative group and 41% in the imaging positive group (p=0.008). The overall and disease-related survival was not significantly different from each other for

the imaging negative patients, but it was significantly better when compared to the same results for the imaging positive patients (Table 5 and Figure 2). Imaging negative patients had an overall 20-year survival of 71% compared to 58% for the imaging positive patients and the disease-related survival was 88% compared to 73% (p=0.015).

Discussion

At the 100th annual meeting of the American Surgical Association in 1980, Dr. Robert Zollinger in the discussion of his paper on the 25 year appraisal of his surgery in patients with ZES [35] stated: "We have to convince our physician friends that it is time to recommend that every gastrinoma be considered a surgical problem. They should not treat the patient with cimetidine indefinitely. It is a basic principle to take out the malignant tumor rather that to treat the end result". Unfortunately, a number of features of ZES/gastrinomas have led a number of groups to not heed Dr Zollinger's advice and instead to advocate over the intervening years a completely medical approach or one in which only patients who had imaged possible primary tumors undergo surgical exploration for possible cure[89101112131415]. The ZES/gastrinoma features that encouraged this approach included: the development of highly successful medical treatment for the gastric acid hypersecretion [1231-3]; the failure to image primary tumors in 30-70% of patients in different series, especially those with duodenal primaries [456,36,37]; the fact that only 20-30% of gastrinomas pursue an aggressive course [38,39]; and that until recently the lack of prospective studies showing surgery could cure a significant number of these patients, effect the development of liver metastases or survival [40]. Other factors favoring a decrease in the use of early surgery for possible cure in these patients included a long delay in the diagnosis of ZES which is a mean >5 years in some studies [12,19,20], and likely increasing with the widespread use of PPIs[16]; and the delay in time from diagnosis to surgery of 4-8 years in some studies [19]. Recent studies have somewhat dealt with a number of these points in that they report immediate postoperative cure rates in sporadic ZES patients of 50-60% and long term cure rates of 30-40% [56,19]; an increase in survival of patients undergoing surgical resection [29] and a decrease in the development of liver metastases [18,29], which are the most important prognostic factor for survival[7,39]. Nevertheless, a recent study [3] reports that the above mentioned factors leading to delays in surgery are still operative in that they conclude from an analysis of their patients diagnosed and treated during different time periods, that at present these patients are being operated later in their disease course with more advanced disease in this era of PPI treatment. [5,7,19,23,26,34,36,39,41,42]

The present study attempts to address one of the important implicit premises of the avocation of only recommending operation for image positive patients (i.e., that surgery is less effective in imaging negative ZES patients) by comparing results of 58 patients with negative imaging to 117 patients with positive imaging operated over the same time period. While the study concludes that surgery in imaging negative patients is just as likely to find a primary gastrinoma, the cure rate is as high, and the survival is even better that in the imaging positive patients, there are a few points that could lead to questioning the result. First, one could argue that insignificant number of patients had endoscopic ultrasound (EUS) that has been identified as one of the best studies to localize pancreatic neuroendocrine tumors [37, 44,45]. However, in this study in the imaging negative patients duodenal gastrinomas were much more frequent (4-fold) than pancreatic gastrinomas, which is similar to other recent studies [41-44]. Numerous studies show that EUS does not visualize most duodenal gastrinomas [44,45] seeing only 35% in one review of five series [37]. Furthermore, all of these patients had careful endoscopic examination of the duodenal area to attempt to identify any submucosal gastrinoma [45]. In addition, intraoperative ultrasound has also been poor at imaging duodenal gastrinomas [42]. This may be because the duodenum has a mixed background with solid, liquid and gas in which it is difficult to detect sonolucent

neuroendocrine tumors like gastrinomas. Therefore, this data supports the conclusion that even if EUS were performed prospectively on these patients it would not have identified a significant additional number of patients preoperatively. Furthermore, it could be argued if SRS was performed in those operated on, before it became available, that additional duodenal lesions might have been detected and therefore the results are not applicable to the present time, during which it is available. This cannot be completely refuted, however, 40% of our patients had negative SRSs in the present study, and furthermore, the SRS frequently misses small duodenal tumors and therefore, because most patients had small duodenal primaries it would have been positive in <50% even if used [4]. Somatostatin receptor scintigraphy has been reported to be the single best preoperative localization study for gastrinoma. It has been able to detect approximately 30% of gastrinomas less than 1 cm, 64% between 1 and 2 cm and 96% of those greater than 2 cm. Because, it is a total body exam, it is especially useful for ectopic (extra-pancreatic, extra-intestinal) gastrinomas [423]. This study corroborates those results because 13 patients (10%) in the imaging positive group had extra-pancreatic, extra-intestinal gastrinoma in ectopic locations including the heart, liver and ovary, while none in the imaging negative group had similar findings.

This is the first study in ZES that has focused on results in imaging negative patients. A common question by patients and referring physicians is why do surgery on these patients with negative imaging studies when they are so well controlled on PPIs? The demographic characteristics of patients with negative imaging studies are remarkably similar to those with imaging positive tumors except they have lower fasting serum gastrin levels and less prior surgery for uncontrolled symptoms of ZES. Further, they have a longer time interval from their disease onset to surgery suggesting that the referring physicians were reluctant to allow them to have surgery. In some studies[21] the level of fasting gastrin correlates with gastrinoma size or tumor burden therefore the finding of lower preoperative fasting gastrin levels in the imaging negative patients is consistent with our finding at surgery of smaller tumors in the majority of these patients. The fact that they have had less surgical procedures for complications of ZES is also consistent with smaller tumor burden. This was also demonstrated in the size of tumors removed during surgery that were significantly smaller in the imaging negative group. Further, in this study there was an equal ability to find tumor in the imaging negative group as in the imaging positive group. The location of the primary tumor in the imaging negative group was most often in the duodenum suggesting that the critical maneuver to finding imaging negative gastrinomas is duodenotomy at the time of surgery [42,43]. The imaging negative group had less other tumors, less pancreatic tumors, less unknown locations and less greater than 1 cm tumors explaining the negative imaging as radiographic imaging is most dependent on size. The extent of tumor in the negative imaging group is still very worrisome as 4 had liver metastases and 34% had lymph node metastases and both of these can affect subsequent disease-related survival [197,29,39]. Each of the deaths in the imaging negative patients occurred in patients with liver metastases. The time from onset to surgery was longer in the imaging negative cohort probably because of delay or procrastination related to the negative radiographic imaging. The extent of surgical operation was similar in the two groups except more patients in the imaging negative cohort had Whipple procedures because of more extensive nodal disease with small duodenal primary tumors. The complications were identical and only one surgical death. The most important results are the long-term outcome data based on preoperative imaging positive and negative results. There is no difference in the development of liver metastases in the imaging negative and imaging positive group, but there is a higher overall development post resection of imaged lesions in the preoperative imaging positive group. There is better overall and disease-related survival and a trend to higher cure-rate in the imaging negative group.

This study suggests that ZES patients with negative imaging studies can greatly [19]benefit from surgical exploration. Tumor is almost always found and removed with acceptable morbidity and minimal mortality. Surgeons doing these procedures should focus primarily on the duodenum and the gastrinoma triangle as most tumors will be found there. However, a complete exploration is necessary as liver metastases and body/tail pancreatic tumors still occur, albeit less frequently. Furthermore, it is essential to routinely sample lymph nodes both in peritumoral areas as well as in the pancreatic head area as this may increase the cure rate, has prognostic significance and is the only means of detecting possible lymph node primary gastrinomas [19,46]. Lymph node primary gastrinomas are controversial and may represent a missed duodenal primary with lymph node metastases as some suggest.[46] The non-imaged tumors are small in size and usually occur within the duodenum. A critical maneuver is duodenotomy that allows precise detection of the duodenal tumors [41-44]. They are not ectopic and they have a similar incidence of lymph node and liver metastases. This type of careful meticulous exploration and resection of preoperative imaging negative tumors should result in improved cure-rate and improved long-term overall and disease-related survival. This happens because negative imaging is associated with a lower incidence of subsequent tumor recurrence.

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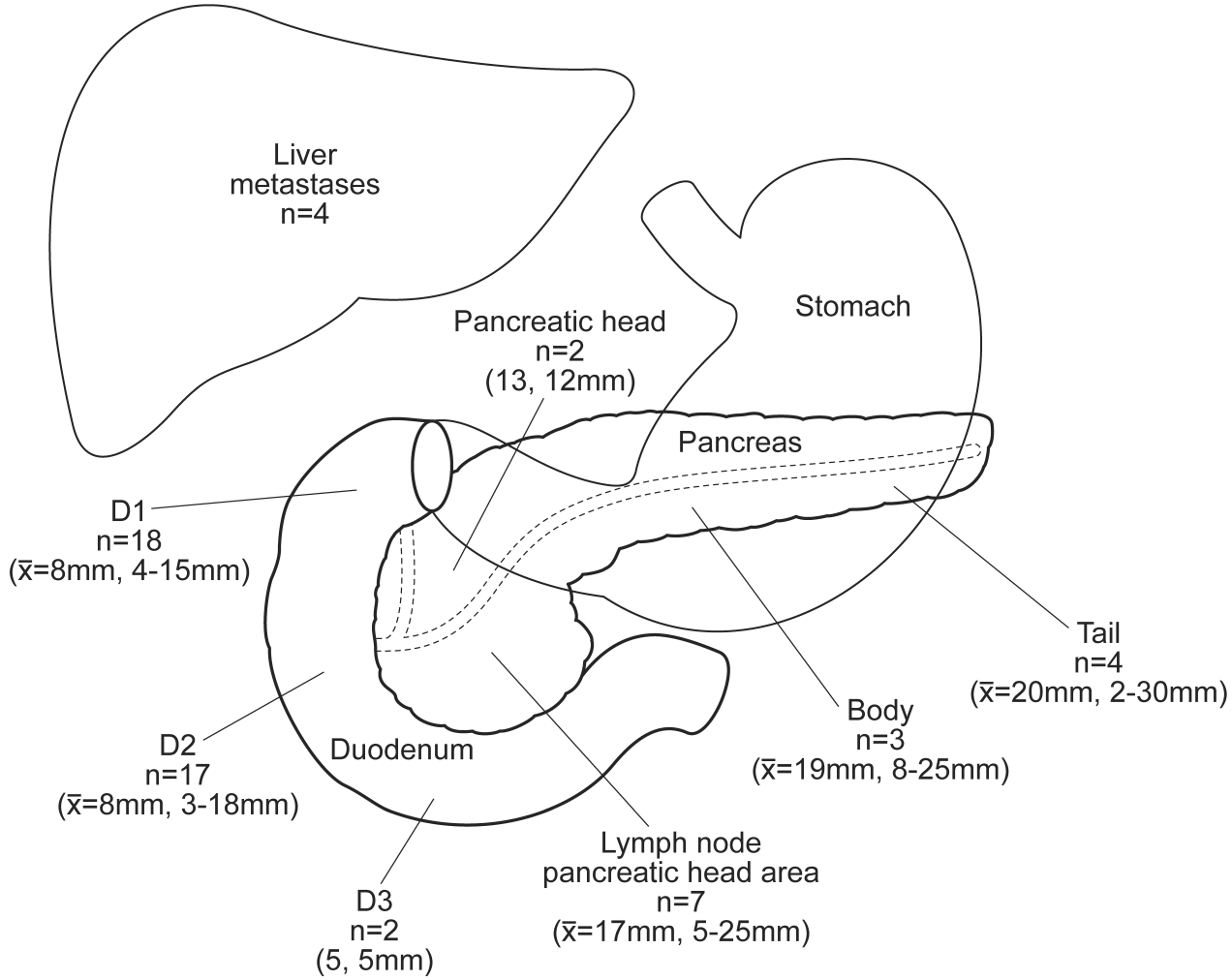

Figure 1.
The exact distribution of the non-imaged gastrinomas.

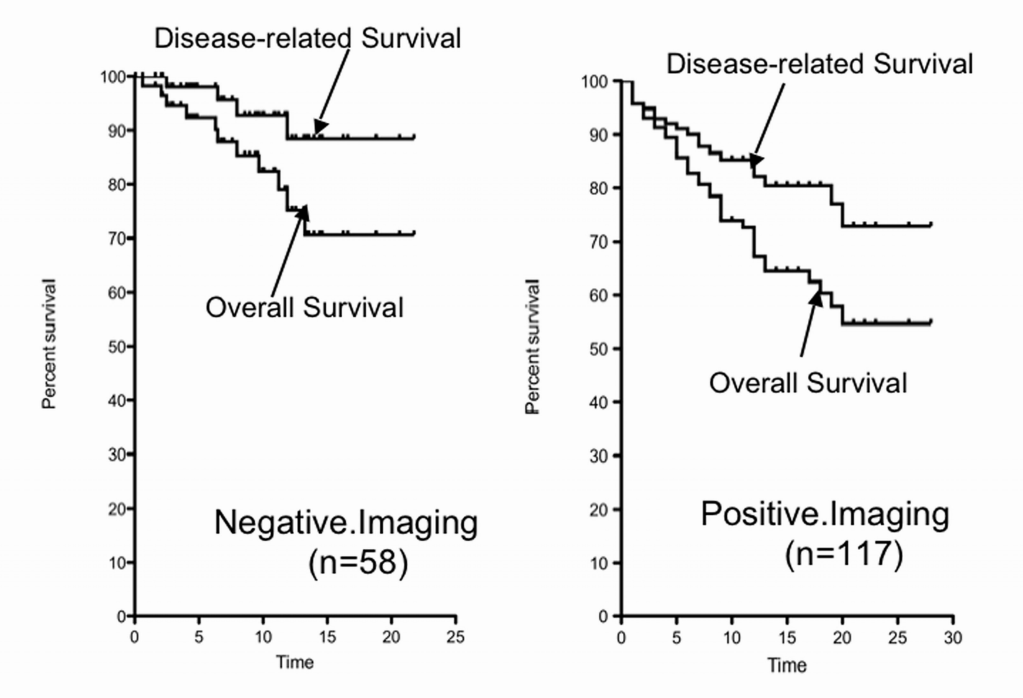

Figure 2.

Kaplan Meier plot of the disease-related and overall survival for the imaging negative and imaging positive. Imaging negative patients had an overall 20-year survival of 71% compared to 58% for the imaging positive patients and the disease-related survival was 88% compared to 73% (p=0.015).

Table 1

Comparison of Patient Clinical Characteristics and laboratory results preoperatively in patients with or without imaging positive studies.

Characteristic	Number (%)		
	IMAGE NEG	IMAGE POS	Significance
Total number	58	117	
Male	33 (57%)	76 (65%)	NS
Ages (yrs)			
Age ZES onset (yrs)			
Mean ± SEM	42.6 ± 1.6	41.7 ± 1.1	NS
[range]	[14.3-64.9]	[11.0-64.6]	
Age ZES Diagnosis (yrs)			
Mean ± SEM	48.8 ± 1.4	47.8 ± 0.9	NS
[range]	[14.2-67.9]	[15.0-69.4]	
Main Presenting symptoms (%)			
Pain	48(83%)	101(86%)	NS
Diarrhea	46 (79%)	94 (80%)	NS
GERD	32 (55%)	44 (38%)	NS
MEN1 present	0 (0%)	0 (0%)	NS
Previous abdominal surgery	6 (10%)	51(44%)	<0.0001
Acid related surgery	2 (3.4%)	25(21%)	0.0021
Hiatal hernia repair	5 (8.6%)	1(0.8%)	0.0081
Other	1 (1.7%) *(a)*	27 (23%) *(a)*	<0.0001
Fasting gastrin level (pg/mL)			
Mean ± SEM	1198 ± 449	3713 ± 1555	
median	522	673	
[range] >10-fold increased	[144-26,000] 9 (15.5%)	[78-175,300] 40 (34%)	0.0099
Delta Secretin			
Mean ± SEM	4558 ± 2370	4590 ± 1188	NS
median	657	806	
[range]	[88-103,000]	[40-101,650]	
BAO (mEq/Hr)			
Mean ± SEM	42.8 ± 2.9 *(b)*	46.6 ± 2.4 *(b)*	NS
[range]	[17.9-95]	[11.1-159]	

(a) 1 patient in imaging negative group had l nephrectomy for renal cell cancer. In the imaging positive group 3 had a colectomy for colon cancer, 8 had an appendectomy, 5 hysterectomy, 5 cholecystectomy, 2 negative laparotomy for PET, 2 for small bowel obstruction, 1 for renal cell cancer, 1 for small bowel perforation after radiological procedure.

(b) Basal acid output data are shown for patients without previous acid related surgical procedures and include data from 49 patients in imaging negative and 95 patients in imaging positive groups.

Table 2

Surgical/pathology findings.

Characteristic	Number (%)		
	IMAGE NEG	IMAGE POS	significance
Patient number	58	117	
PET found at surgery	57 (98%)	106 (90.5%)	0.059
Primary PET location (surgery)			
Location			
Pancreas	9 (15.5%)	35 (30%)	0.039
Duodenum	37 (64%)	43 (37%)	0.0008
Lymph node [a]	7 (12%)[a]	13 (11%)[a]	0.85
Other[b]	0 (0%)	13 (10.2%)[b]	0.008
Unknown[c]	5 (8.6%)[c]	24 (20.5%)[c]	0.047
>1 primary tumor	0 (0%)	7 (6%)	0.0036
Primary tumor size (cm)			
Mean ± SEM	1.09 ± 0.09	1.9 ± 0.2	<0.01
[range]	[0.2-3]	[0.4-8]	
≤ 1 cm	36 (62%)	24 (20.5%)	<0.00001
≥3 cm	1 (1.7%)	21 (18%)	0.0024
Tumor extent at surgery			
Primary only	28 (54%)	45 (38%)	0.21
Primary plus lymph node involvement	20 (34%)	51 (44%)	0.25
With liver involvement ± lymph node involvement	4 (6.8%)	9 (7.7%)	0.83
Lymph node metastases only	4 (6.8%)	11 (9.4%)	0.57

[a]Primary lymph node gastrinoma was defined as previously reported and included a patient in which only lymph nodes (s) were removed who had normal fasting gastrin levels, secretin test result, and imaging postoperatively. (see reference 46)

[b]Other primary locations includes in the imaging positive group 13 patients with primary tumors in: ovary (n=1),; liver (n=4); pylorus (n=2); heart (n=1); common bile duct (n=2); omentum (n=2); lung cancer (n=1) .

[c]Unknown includes in the imaging negative and positive groups, respectively: 4 and 11 patients with only lymph node metastases; 0 and 2 patients) with only liver metastases, found determined as described in Methods and 1 and 11 patients with no tumor found.

Table 3

Surgical procedures and complications.

Characteristic	Number (%)		
	IMAGE NEG	IMAGE POS	significance
Patient number	58	117	
Time to onset ZES to surgery (yrs)			
Mean ± SEM	8.9 ± 1.1	7.6 ± 0.6	
Time>10 yrs	22 (38%)	29(25%)	0.036
Age Surgery (yrs)			
Mean ± SEM	51.3 ± 1.4	48.9 ± 1.0	NS
[range]	[26.2-71.0]	[14.6-73.3]	
Type Primary surgery			
Biopsy only	0 (0%)	4 (3.4%)	0.15
Enucleation	6 (10.3%)	12 (10.2%)	0.99
Resection	49 (84%)	101 (86%)	0.74
Partial pancreatectomy	6 (10.3%)	13 (11%)	0.88
Whipple resection	4 (6.8%)	1 (0.8%)	0.024
Liver resection	3 (5.2%)	18 (15%)	0.051
Wedge resection	2 (3.4%)	7 (6%)	0.47
Lobectomy/segmentectomy	1 (1.7%)*(a)*	11 (9.4%)	0.059
Surgical complications			
Surgical death	0 (0%)	1 (0.8 %)*(a)*	0.47
Complications	20 (34%)*(b)*	40 (34%)*(b)*	0.96

(a) One patient in the imaging positive group died postoperatively from a pulmonary embolus.

(b) Complications for the imaging negative and positive groups include respectively; pancreatitis (5,3); abscess (1,10); fistula (2,18); pneumonia (2,2); postop motility disorder (2,2); phlebitis (1,5); wound infection (4,6); hepatitis (1,0); postoperative bleeding (0,1).

Table 4

Postoperative course, surgical result and follow-up.

Characteristic	Number (%)		
	IMAGE NEG	IMAGE POS	significance
Patient number	58	117	
Status Last follow-up			
Alive	47 (81%)	79 (67%)	0.062
Dead	11 (19%)	38 (32%)	
Disease-related death	4 (6.9%)	20 (17%)	0.066
Years surgery to death			
Mean ± SEM	4.3 ± 1.3	8.1 ± 0.6	0.01
[range]	[0.6-13.2]	[0.6-20.7]	
Years surgery to disease-related death			
Mean ± SEM	7.2 ± 1.9	7.1 ± 1.3	0.99
[range]	[2.4-11.9]	[0.6-20.7]	
Duration of follow-up (yrs)			
Time from surgery to last follow-up (yrs)			
Mean ± SEM	9.5 ± 0.7	11.6 ± 0.6	
[range]	[0.1-21.8]	[0.1-28.1]	
Time from onset ZES to last follow-up (yrs)			
Mean ± SEM	18.8 ± 1.2	19.2 ± 0.9	
[range]	[4.2-49.5]	[1.4-42.1]	
Postoperative status			
Disease-free			
Immediate Postop	36 (63%)	63 (54%)	0.31
Last Followup	28 (48%)	41 (35%)	0.09
Not disease free last followup	30 (52%)	76 (64%)	0.09
Recurrence	8 (14%)	22 (19%)	0.41
Liver metastases during follow-up			
No. developing liver metastases	6 (10%)	19 (17%)	0.36
Time to development (yrs)			
Mean ± SEM	3.7 ± 0.9	3.1 ± 0.6	
[range]	[0.8-7.2]	[0.2-7.2]	
No. developing new lesions during follow-up	12 (21%)	48 (41%)	0.008

Table 5

Survival: Overall and Disease-related.

	% Survival [95 % CI](1)		
A. Imaging Negative (n=58) ((2),(4))	**5 yrs**	**10yrs**	**20 yrs**
Total survival	90 [78-96]	82 [68-91]	71 [51-83]
Disease-related survival	98 [83-99]	93 [79-98]	88 [71-96]
B. Imaging positive (n=117) ((3),(4))			
Total survival	86 [77-91]	74 [64-81]	58 [46-68]
Disease-related survival	91 [84-95]	85 [76-91]	73 [58-83]

(1)Percentage survival from surgery calculated from data from 58 patients with negative imaging preoperatively and 117 patients with positive imaging from survival curves shown in Fig. 2.

(2)For the Imaging Negative patients during the followup (9.5 ± 0.72 [range-0.1-21.8 yrs] from surgery, 11 patients died from any cause (overall survival)(Fig.1) and 4 died from a Disease-related cause (Fig. 1).

(3)For the Imaging Positive patients during the followup (11.6 ± 0.6 [range-0.1-28.1 yrs] from surgery, 38 patients died from any cause (overall survival)(Fig.1) and 20 died from a Disease-related cause (Fig. 1).

(4)The differences between the Overall survival and Disease-related survival were not significant (p=0.069, HR-2.56, 95 CI-0.92-7.1) for theImage Negative patients. Howcver, they were significantly (p=0.015, HR-1.93, 95 CI-1.14-3.2) different from the Image positive patients