

# Changing Treatment Strategy for Gastrinoma in Patients with Zollinger-Ellison Syndrome

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## Abstract

We overviewed the recent development of curative surgery for gastrinoma that has been rapidly improved since the development of new localization techniques, especially the selective arterial secretagogue injection test (SASI test) and somatostatin receptor scintigraphy (SRS). A number of new pathological findings of gastrinomas in patients with Zollinger-Ellison syndrome have been accumulated in accordance with the increase of curative resection of gastrinomas, and these new findings also have contributed to the progress of the treatment strategy for gastrinomas.

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Until recently, medical treatment with a proton pump inhibitor or an H<sub>2</sub> blocker has been the treatment of choice for patients with Zollinger-Ellison syndrome (ZES) because of the difficulty in accomplishing curative resection of gastrinomas, which are often metastatic and multiple. Symptoms of ZES, such as persistent peptic ulcer, regurgitation esophagitis, or diarrhea, appear even when the gastrinoma is too small to be recognized with computed tomography (CT) or magnetic resonance imaging (MRI),<sup>1–12</sup> and localization of small functioning gastropancreatic-endocrine tumors (GEPET) has been unsuccessful.<sup>1–4</sup> All gastrinomas are potentially metastatic. Liver metastases are the significant prognostic factor in patients with gastrinoma, and only R0 resection can achieve a disease-free survival.<sup>2–17</sup> For all of these reasons, curative resection of gastrinomas guided by an accurate localization technique has long been awaited. Such a technique has been realized with the development of the selective arterial secretagogue injection test (SASI test) with secretin or calcium and somatostatin receptor

scintigraphy (SRS).<sup>2–6,14–17</sup> Increased curative resection surgery for gastrinomas in patients with ZES has elucidated several important findings.

In patients with ZES without multiple endocrine neoplasia type 1 (MEN-1), gastrinoma is located in either the duodenum or the pancreas. In either location, gastrinomas are often single, but occasionally they co-exist. In the most recent reports, duodenal gastrinoma is reported more frequently than pancreatic gastrinoma.<sup>2–12</sup>

In patients with ZES and MEN-1, gastrinoma is located mostly in the duodenum, although there are numerous endocrine tumors in the pancreas. In about a half of these patients, multiple duodenal gastrinomas are diffusely located in the duodenum and sometimes they are numerous.<sup>6,9–24</sup>

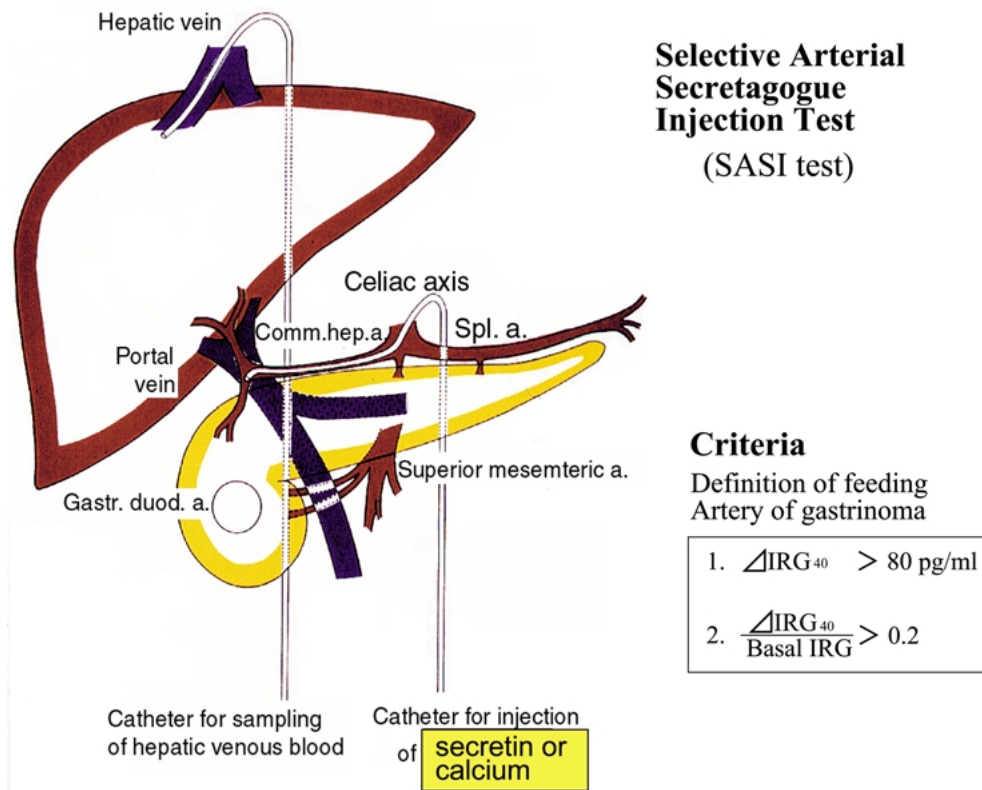
Incidence of lymph node metastases in patients with either duodenal or pancreatic gastrinomas has been reported to be greater than 40%.<sup>19–27</sup>

The incidence of hepatic metastases has been reported to be more than 60% in patients with the pancreatic gastrinoma, although it has consistently been less than 10% in patients with duodenal gastrinoma.<sup>11,22–27</sup>

Liver metastases are a significant prognostic factor in patients with gastrinoma. Therefore accomplishing a curative resection before liver metastases can develop is

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**Figure 1.** Schema of the SASI test.

important for disease-free survival.<sup>6,12–19,24–26</sup> The treatment strategy for gastrinoma in patients with ZES has to be decided considering these findings, and the modus of resection surgery is based on correct localization of the gastrinoma(s).

## LOCALIZATION

Sensitivity of CT, ultrasound (US), MRI, and abdominal arteriography (SAG) has been reported to range between 40% and 70%.<sup>2–8,11,12</sup> None of these diagnostic modalities can diagnose duodenal gastrinomas <5 mm, and all of them can visualize only 15%–30% of pancreatic gastrinomas between 1 and 3 cm in diameter.<sup>26</sup> These imaging techniques cannot be relied on for curative resection of gastrinomas.<sup>2,12,13</sup> Similarly, portal venous sampling (PVS) has not predicted the precise location of gastrinomas, and its accuracy rate has been described to be between 30% and 70%.<sup>4,14</sup>

A new technique, the selective arterial secretagogue injection test (SASI test) with secretin or calcium and somatostatin receptor scintigraphy (SRS) represents the most reliable approach to localizing gastrinomas.<sup>2–4,12–20</sup> The guiding principle of the SASI test is localization of gastrinomas by demonstrating a feeding

artery of the gastrinoma. This works because gastrinoma cells release gastrin when stimulated with secretin or calcium, both *in vitro* and *in vivo*.<sup>28–33</sup> With this test, gastrinomas > 1 mm in diameter can be localized, and more than 90% of gastrinomas that are <5 mm in diameter have been correctly localized (Fig. 1).<sup>14,16,30–33</sup>

Somatostatin receptor scintigraphy can be used to localize gastrinomas because almost all gastrinoma cells possess somatostatin receptors on the cell membrane. By injecting the radiolabeled somatostatin analog intravenously, not only the main tumor but also metastatic tumors >2 cm can be visualized with SRS.<sup>20</sup> Somatostatin receptor scintigraphy is the most convenient and useful method to check the distribution of gastrinomas in the whole body of the patient.<sup>12,20</sup> However, because the sensitivity of SRS is correlated with the size of the gastrinoma, only 30% of gastrinomas <1 cm in diameter can be visualized by this technique. Furthermore, SRS visualizes various kinds of gastropancreatic endocrine tumors only if they have somatostatin receptors, and the differential diagnosis of gastrinoma from other GEPET is difficult with SRS. For this purpose we have performed the SASI test as a new tool in diagnosing gastrinomas.<sup>2–4,14–17</sup>

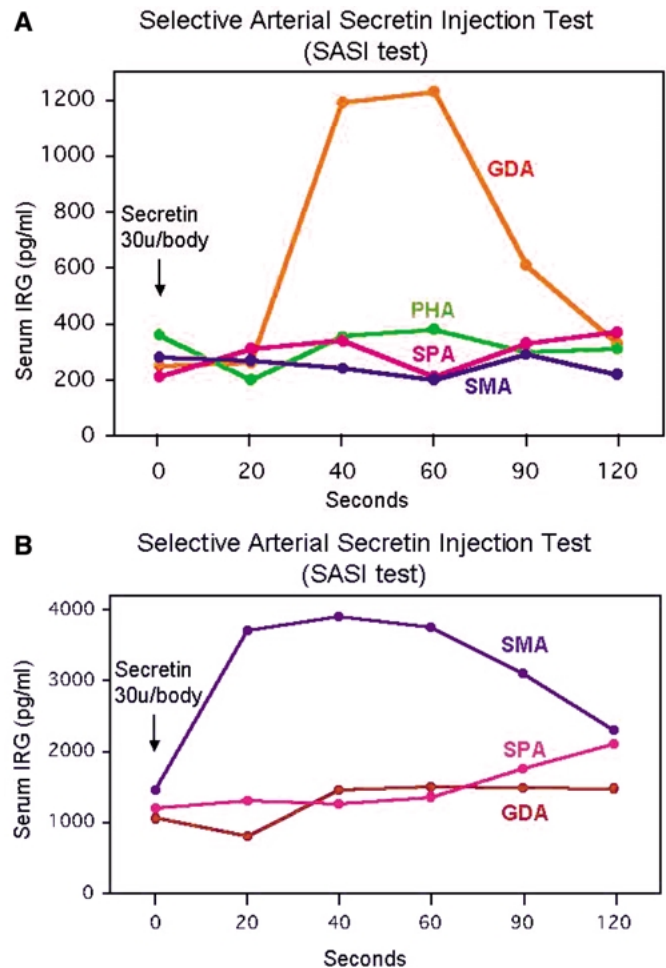
## SELECTIVE ARTERIAL SECRETAGOU INJECTION TEST (WITH SECRETIN OR CALCIUM): SASI TEST

The selective arterial secretagogue injection test was described in 1987.<sup>2</sup> At the time of abdominal arteriography, 30 U of secretin in 2 ml solution are injected into each artery that feeds the pancreas and/or the duodenum (the splenic artery or the gastroduodenal or the superior mesenteric artery) and 2 ml of blood samples are drawn from the right or the left hepatic vein through a catheter inserted via the femoral vein before and 20, 40, and 60 seconds after the injection. The changes in hepatic venous serum immunoreactive gastrin level (HV-IRG) are measured. When the rise of the HV-IRG at either 20 or 40 seconds was more than 80 pg/ml and more than 20% from the basal IRG, the artery is determined to be the feeding artery of the gastrinoma. So we can locate a gastrinoma(s) by demonstrating the feeding artery. More precise location can be diagnosed by injecting secretin into the each peripheral branch of either the superior mesenteric artery or the gastroduodenal artery. When the splenic artery was the feeder, more precise localization is possible by injecting secretin from a different point of the splenic artery (Fig. 2a, 2b).

Hepatic metastasis can be diagnosed by taking the blood samples from both the right and the left hepatic vein after an injection of the secretagogue into the proper hepatic artery. In most patients with ZES, secretin is useful as the secretagogue, but in less than 10% of patients with ZES, secretin is not useful for releasing gastrin from the gastrinoma.<sup>32</sup> In such cases, calcium solution (1 ml of 8.5% calcium gluconate) can be used, although in most cases the extent of response of the gastrinoma cells to calcium is milder than the response to secretin.<sup>30,32</sup> Both the specificity and the sensitivity of the SASI test is greater than 90%. Thus, the SASI test has been the most reliable localization technique for the curative resection of the gastrinoma.

## SOMATOSTATIN RECEPTOR SCINTIGRAPHY: SRS

Radiolabeled octreotide ( $[^{111}\text{In-DTPA-D-Phen}^1]$  octreotide) can visualize gastropancreatic endocrine tumors > 3 cm.<sup>20</sup> Almost all gastrinoma cells have somatostatin receptors, so SRS can detect not only gastrinomas around the pancreas, but also metastatic gastrinomas in the whole body. It is the most useful technique for detecting the ectopic gastrinoma.<sup>34</sup> Somatostatin recep-



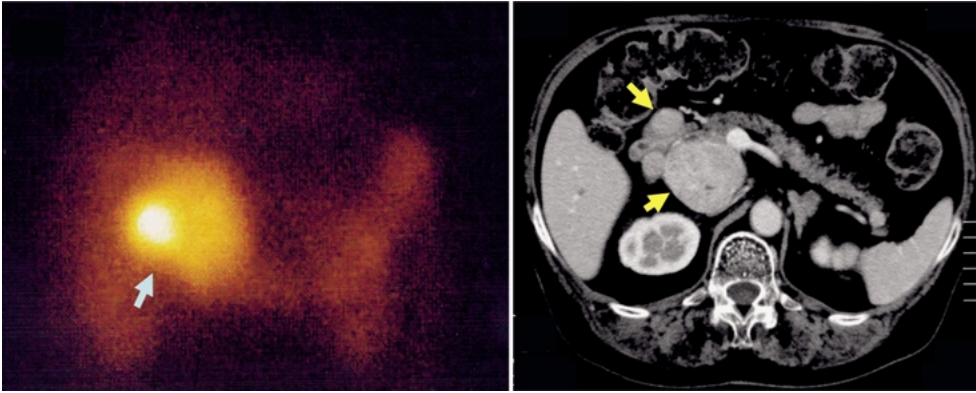
**Figure 2.** A. The SASI test revealed that the gastroduodenal artery (GDA) is a feeding artery of the gastrinoma, indicating that the gastrinoma(s) is located in the upper part of the pancreas or the duodenum. A gastrinoma in the upper part of the duodenum was found and resected at operation, and the patient has remained disease free. B. The SASI test showed that the superior mesenteric artery is a feeding artery of the gastrinoma, indicating that the gastrinoma(s) is located in the lower part of the pancreas or the duodenum.

tor scintigraphy is an easy examination for patients and indispensable for estimating the extent and the stage of the gastrinoma (Fig. 3).

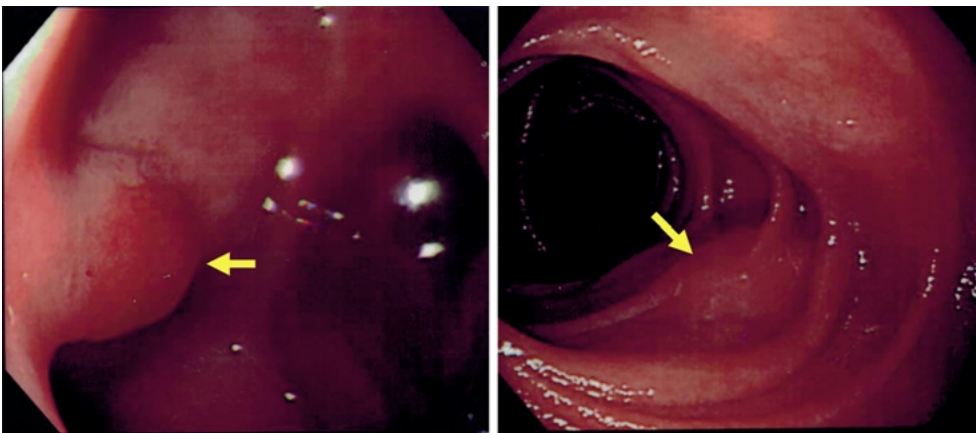
## INTRAOPERATIVE LOCALIZATION METHODS

### Intraoperative Ultrasonography: IOUS

Pancreatic tumors >5 mm in diameter can be localized with IOUS.<sup>4-6</sup> One thing that we have to be concerned



**Figure 3.** Somatostatin receptor scintigraphy and computed tomography in a patient with a pancreatic gastrinoma and a large metastatic lymph node at the pancreas head.



**Figure 4.** Intraoperative duodenoscopy in a patient with multiple endocrine neoplasia type 1 (MEN-1) and Zollinger-Ellison syndrome (ZES); multiple duodenal tumors are apparent.

about is that the visualized tumor may not be a gastrinoma, and the intraoperative pathological study is intended for confirmation of the gastrinoma. Gastrinomas are often multiple and metastatic, so the intraoperative secretin test (IOS test) is recommended for estimating curability of the resection surgery. Resection of only one or two tumors may not be enough for the curative resection.<sup>14–17</sup>

### Intraoperative Duodenoscopy: IDS

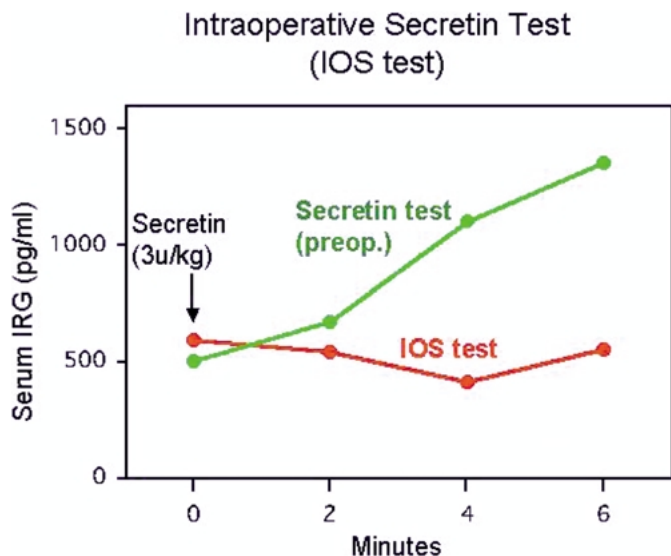
Precise endoscopic examination of the whole duodenum (IDS) can be performed only intraoperatively.<sup>11,14</sup> A surgeon can guide the introduction of the duodenoscope into the duodenum and manipulate it effectively during surgery. A duodenal gastrinoma looks like a submucosal tumor with a central depression. There are various kinds of submucosal tumor or lesions other than gastrinomas in the duodenum, for example, an ectopic pancreas, enlarged Brunner's glands, or ulcer scars. It is therefore important to confirm the pathology of the resected tissues during surgery (Fig. 4).<sup>4–6,23</sup>

### INTRAOPERATIVE SECRETIN TEST: IOS TEST

As already mentioned, the IOS test is recommended for estimating curability of the resection surgery.<sup>14,16,35</sup> The IOS test is performed once before and three times after resection of the tumors. After the injection of 3 U secretin per kg body weight into a subcutaneous vein, 2 ml of peripheral venous blood is drawn before, and 2, 4, and 6 minutes after the injection. When the post-resection result of IOS becomes negative, the resection is considered to be curative (Fig. 5).

### INDICATION FOR SURGICAL RESECTION

Surgical resection of the gastrinomas is indicated when the preoperative CT or SRS study did not reveal any distant metastasis.<sup>6,14–18</sup> For hepatic metastases, even individual ones, macroscopic curative resection is recommended, because its use is associated with a higher incidence of long-term survival.<sup>7,36,37,38</sup> When there are



**Figure 5.** The intraoperative secretin (IOS) test. In this patient, the preoperative IOS test was positive and became negative after resection of gastrinomas. The surgery was therefore estimated to have been curative.

only one or two brain metastases, treatment with the Gamma knife is recommended. For the multiple duodenal gastrinomas in the patient with MEN-1, pancreas preserving total duodenectomy (PPTD) should be considered as one of the choices.<sup>39</sup>

### **SURGERY FOR GASTRINOMAS IN PATIENTS WITHOUT MEN-1 (SPORADIC GASTRINOMA)**

There is no controversy regarding the selection of surgery when there is no distant metastasis in patients with sporadic gastrinoma.<sup>6-14,35</sup> In these patients, gastrinomas are located either in the pancreas or the duodenum (Fig. 6), and recently the duodenal gastrinoma has been reported more frequently than the pancreatic type.<sup>6-14</sup> The incidence of liver metastasis from pancreatic gastrinoma is higher than from duodenal gastrinoma, although in either case, the incidence of lymph node metastases has been reported to be more than 40%.<sup>6,9,10</sup> In 80% of patients with sporadic duodenal gastrinoma, resection of a single duodenal gastrinoma with dissection of the regional lymph nodes has been sufficient for cure; in the other 20% of these patients, either there are multiple duodenal gastrinomas or a combination of duodenal and pancreatic gastrinomas.<sup>2,3,7-15</sup> As the preoperative SASI test is the most

reliable localization method, it is reasonable to guide surgery based on localization with the SASI test.<sup>2,3,4,14-17</sup>

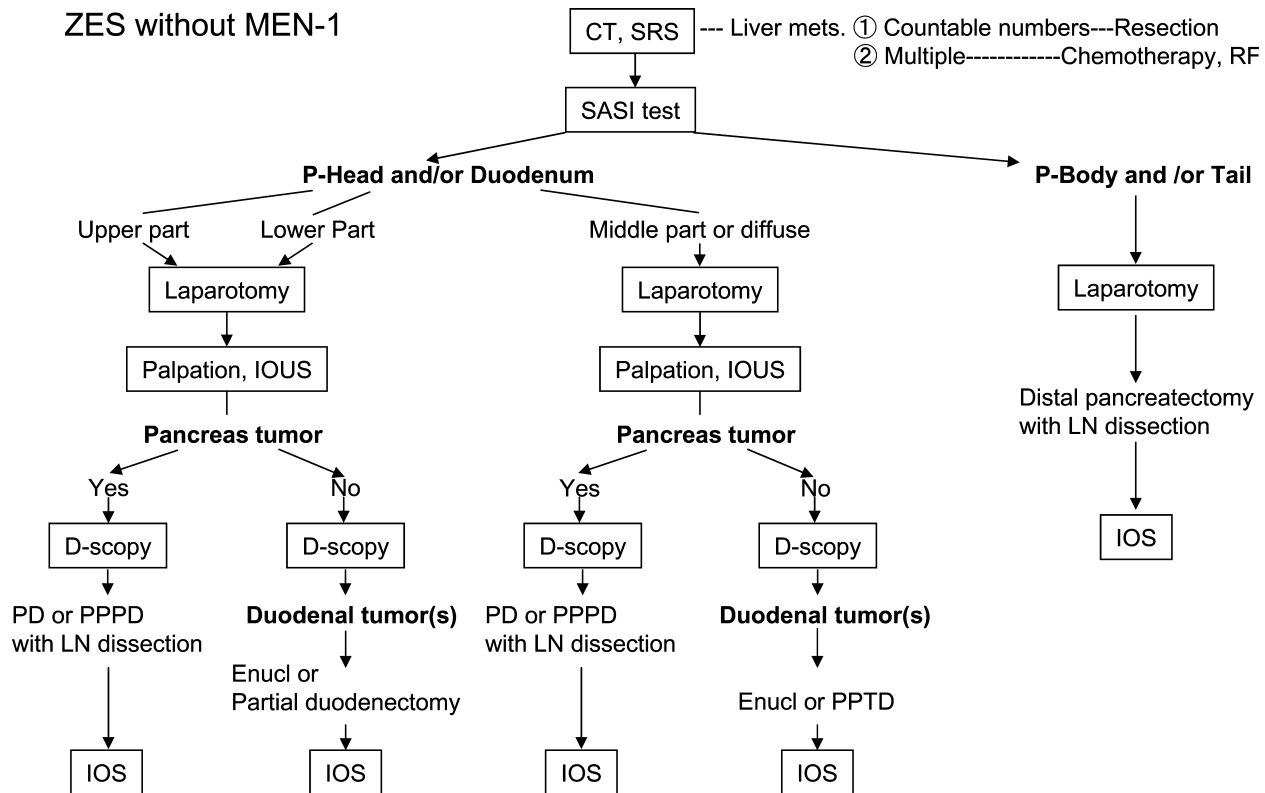
### **CURATIVE RESECTION OF GASTRINOMAS**

#### **When the SASI Test Localizes Gastrinomas in the Head of the Pancreas or the Duodenum**

In cases where the SASI test has confirmed the presence of gastrinomas in the head of the pancreas or the duodenum, laparotomy is performed and the head of the pancreas is examined carefully, both by palpation and with US. The duodenum is also examined by palpation after Kocher's mobilization and with IDS. For patients with pancreatic gastrinoma(s) without the duodenal tumor, pylorus-preserving pancreatoduodenectomy (PPPD) is indicated. Very few patients who have both duodenal and pancreatic gastrinomas have been reported.<sup>2,3,14,17,24</sup> For these patients, pancreatoduodenectomy (PD) is indicated. Lymph node dissection is important and should be performed according to the method of D2 lymph node resection for pancreatic ductal adenocarcinoma, with sampling of the para-aortic lymph nodes.<sup>2,3,11,14,17,24</sup>

When no tumor is found in the head of the pancreas, the whole duodenal mucosa should be examined with IDS and secondarily by palpation of the mucosa with the surgeon's index finger through a duodenal opening.<sup>6</sup> Any suspected duodenal tumors are enucleated and the specimens are sent to the pathologist for diagnostic confirmation of endocrine tumor.<sup>7-13</sup> After the resection, curability should be confirmed with the IOS test.<sup>35</sup> For patients treated between 1981 and 1988 in whom no tumor was identified with these procedures in spite of localization with the SASI test, we performed PD.<sup>2,3</sup> During that period duodenal gastrinoma was not yet regarded as an important cause of ZES.<sup>2-8</sup> In the early four patients who underwent PD in Kyoto University Hospital, 1-7 minute duodenal gastrinomas were found in the resected specimen, although none had been detected during surgery. At that time there were many surgeons who hesitated to do PD for these patients, because PD seemed to be too invasive for this disease.<sup>18</sup> But some aggressive surgeons performed PD and achieved a high rate of curability with low morbidity.<sup>2,3,7-12,17</sup> The experience with PD taught us how difficult was it to find duodenal gastrinomas and metastatic lymph nodes even at operation. But because only the microscopic duodenal gastrinomas had been revealed in the resected specimen only after the PD, we changed our strategy from PD to the

## ZES without MEN-1



Mets: metastasis, RF: radiofrequency ablation, P: pancreas, D: duodeno, IOUS: intraoperative ultrasonography, LN: lymph nodes, IOS: intraoperative secretin test, PD: pancreatoduodenectomy, PPPD: pylorus preserving pancreatoduodenectomy, Enucl. enucleation, PPTD: pancreas preserving total duodenectomy

**Figure 6.** Schema of diagnosis and treatment strategy for patients with sporadic gastrinomas.

transduodenal enucleation of the duodenal gastrinomas. But even after this change, PD or PPPD had to be performed, because the intraoperative identification of duodenal gastrinomas was so difficult in these patients. In 19 patients who underwent surgery in our department, 8 patients received PD, we accomplished seven transduodenal enucleations, one extirpation of the gastrinoma on the upper edge of the pancreatic body, and one PPTD. Since then, 18 patients (94.7%) have remained disease-free from 3 to 14 years, and only one patient with a metastatic para-aortic lymph node at the time of surgery is not cured.<sup>35</sup>

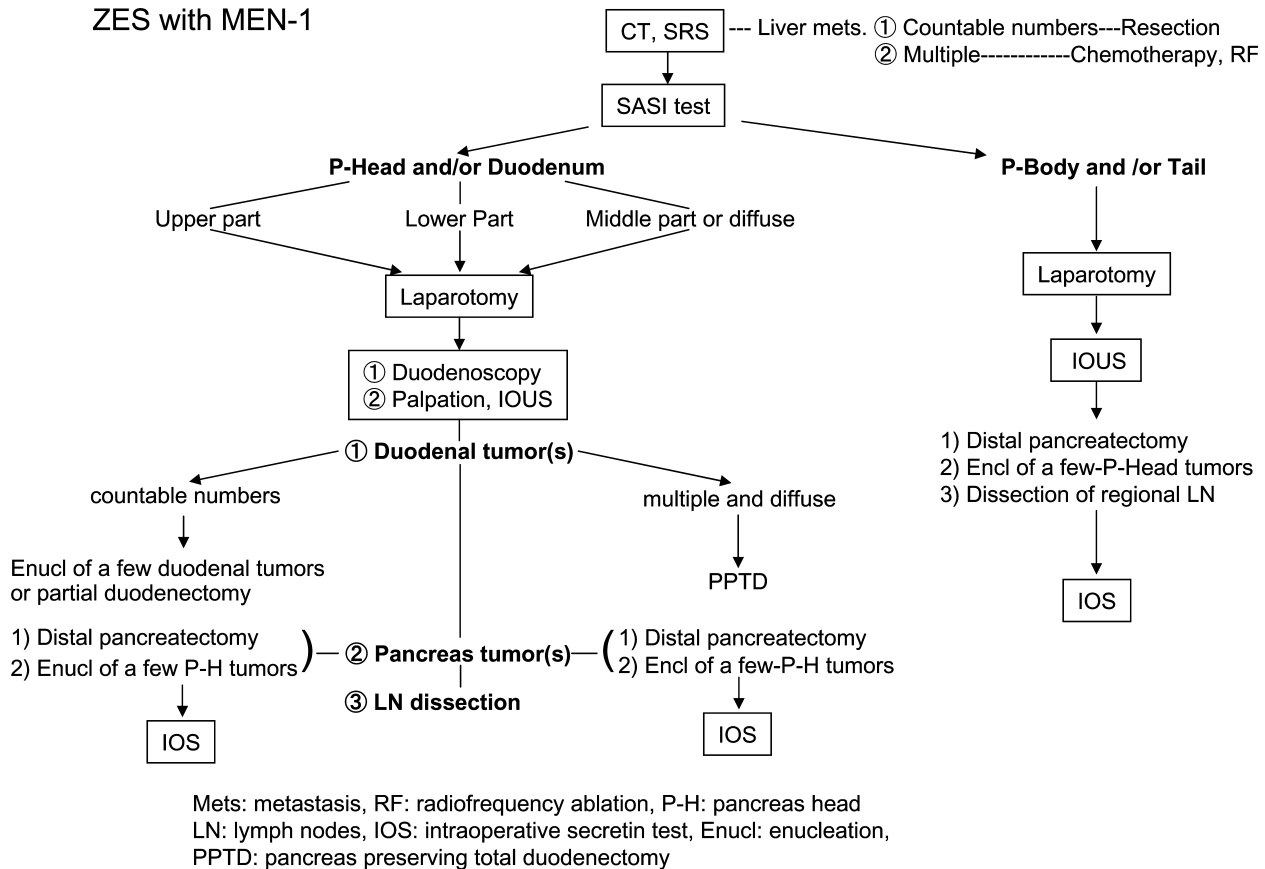
### When the SASI Test Localized Gastrinomas in the Body or Tail of the Pancreas

In the case of documented localized gastrinomas in the tail of the pancreas, distal pancreatectomy with dissection of the regional lymph nodes is performed after the identification of the tumor by palpation or with IOUS.<sup>3,4,7,14</sup>

Use of the IOS test is recommended before closing the abdomen.<sup>14</sup>

## SURGERY FOR GASTRINOMAS IN PATIENTS WITH MEN-1

In patients with MEN-1 and ZES, there are usually a number of microscopic or macroscopic endocrine tumors in the pancreas (Fig. 7), some of which may be visualized with CT or SRS.<sup>22-25</sup> Until recently, these tumors have been resected under the misdiagnosis of gastrinoma. Recent studies have revealed that in MEN-1 patients most pancreatic tumors are endocrine tumors other than gastrinoma, and gastrinomas are predominantly located in the duodenum and are often multiple.<sup>6,14,22-26</sup> Before 1990 it was reported that more than 30% of pancreatic gastrinomas occurred in patients with MEN-1. Since the recognition of the duodenal gastrinomas as the cause of ZES in patients with MEN-1, the incidence of pancreatic



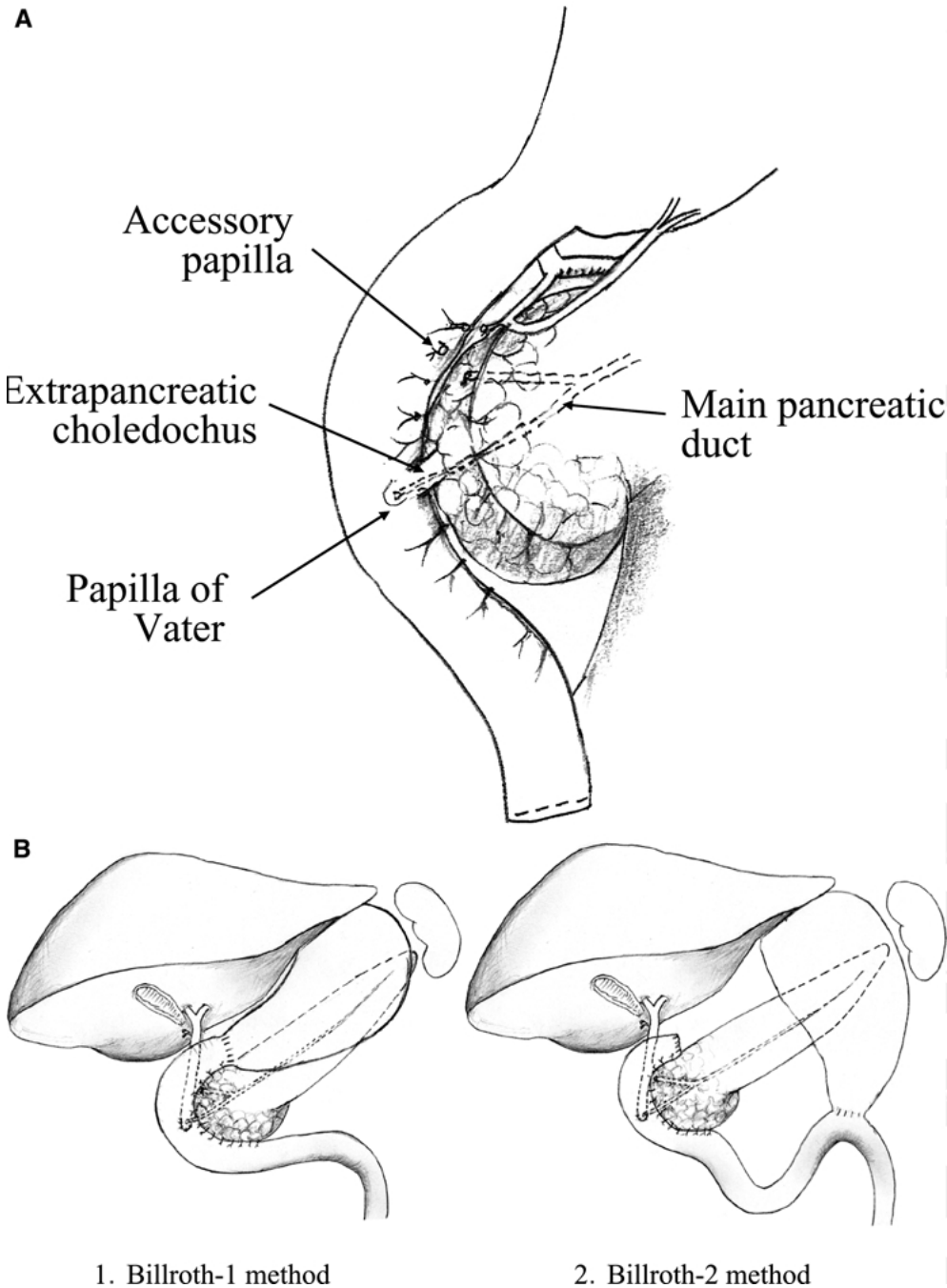
**Figure 7.** Schema of diagnosis and treatment strategy for patients with MEN-1.

gastrinoma has been reported as less than 10%.<sup>22-25</sup> We should be careful about this point, when reading the reports published before 1987 that include patients with MEN-1.<sup>26</sup>

There has been much controversy about whether or not to perform resection of duodenal gastrinomas or to leave them as they are and observe both the duodenal and the pancreatic endocrine tumors until they grow larger than 2 or 3 cm. Doctors at the National Institutes of Health (NIH) reported that none of 10 consecutive patients with MEN-1 and ZES had not been cured by the transduodenal resection, both because there was a high rate (86%) of lymph node metastasis and because 30% of the patients had more than 20 duodenal gastrinomas.<sup>12</sup> These investigators had not performed PD and did not follow the patients who underwent noncurative resection for long because the natural history of these patients remained unclear and surgical resection of all the gastrinomas might not prolong survival.<sup>12</sup> Recently Gibril *et al.* at NIH reported the results of 57 patients with MEN-1 and ZES who had been followed for 8 years without receiving surgery until the pancreatic endocrine tumors grew larger than 2.5 cm.<sup>26</sup> As a result, 13 patients (23%) developed liver metastasis, and three of them (5%) died of their

disease. The surgeons therefore suggested that a more aggressive surgical strategy should be applied, even to patients with MEN-1 and aggressive tumor development.<sup>26</sup>

Thompson, who has applied aggressive procedures, such as transduodenal enucleation of duodenal gastrinomas and subtotal distal pancreatectomy for multiple microscopic or macroscopic tumors, reported that surgery has contributed to survival in 40 patients with MEN-1 and ZES, hypoglycemia, or both.<sup>24</sup> Of 34 patients with ZES, 68% have remained eugastrinemic as long as 19 years. One patient developed a single liver metastasis that was excised without any recurrence.<sup>24</sup> So two-thirds of these patients may have a chance to be cured of ZES only by aggressive resection of the duodenal gastrinoma. We have treated 14 patients with MEN-1, including two patients with diffuse liver metastasis. For 12 patients who had no distant metastasis, we successfully performed curative resections of gastrinomas. According to the localization of SASI test for the first four patients treated between 1986 and 1989 we performed PD. In all four patients the duodenal gastrinoma (seven gastrinomas in one case, two gastrinomas in one, and one gastrinoma in two) was proved in the resected specimen, and three of



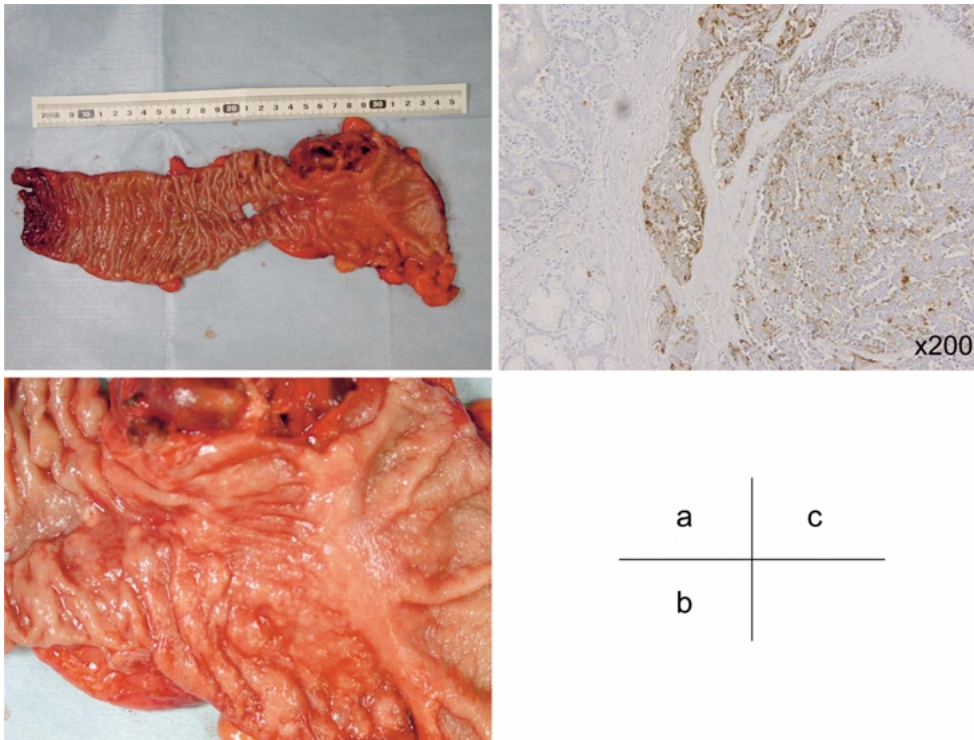
**Figure 8.** Schema of pancreas-preserving total duodenectomy (PPTD). The duodenum is totally resected, saving the whole structure of the major papilla by stripping off its mucosal layer (a). After the incisional papillotomy, the opened distal bile duct is anastomosed to the small incision of the jejunum for reconstruction of the biliopancreatic internal drainage. Reconstruction of the alimentary tract is performed with either by the Billroth-1 or the Billroth-2 procedure (b).

them had lymph node metastases, but no pancreatic gastrinoma was proved. They have been cured as long as 18 years.

Because there was no pancreatic gastrinoma in the resected specimen after PD, beginning in 1990, we changed a mode of operation from PD to the enucleation of duodenal gastrinomas. The next four patients underwent the transduodenal enucleation and/or partial resection of the duodenum. Three of them had multiple duodenal gastrinomas and two had lymph node metas-

tasis. All of them have been cured as long as 15 years. Then we encountered a patient in whom duodenoscopy revealed more than seven duodenal tumors. We performed PPTD instead of PD, and pathological study revealed numerous microscopic duodenal gastrinomas in the resected specimen. This patient has been cured for 1 year.<sup>39</sup>

The PPTD procedure was first performed for a patient with familial adenomatous polyposis in 1995 by Chung *et al.*<sup>40</sup> We performed the first PPTD for a patient with



**Figure 9.** A specimen of the duodenum and a part of the gastric antrum after PPTD. The whole duodenum is resected with the whole of the major papilla. There are numerous mucosal tumors in the duodenum (a). b. A magnified view of the multiple duodenal tumors. Antigastrin serum staining showed gastrin-positive cells in the mucosal tumors (c).

MEN-1 and numerous duodenal gastrinomas with a new technique, in which the whole pancreatic duct is preserved with the papilla of Vater, and the papillectomized bile duct is anastomosed to the jejunum.<sup>39</sup> This is, we believe, safer than previous techniques, because the pancreatic duct anastomosis is not performed (Figs. 8 and 9).

In summary, there are two important issues in dealing with patients with ZES and MEN-1, one is how to perform curative resection for the duodenal gastrinomas and another is how to treat the pancreatic endocrine tumors.

As for treatment of duodenal gastrinoma(s), patients with a single duodenal gastrinoma will be cured by transduodenal enucleation with the dissection of regional lymph nodes. For patients with a few duodenal gastrinomas whose locations are deviated to either the upper or the lower part of the duodenum, partial resection of the duodenum is indicated. For patients with multiple gastrinomas diffusely located throughout the duodenum, PPTD is indicated. In either case, IOS should be performed for confirmation of the curability of the operation.<sup>39</sup>

For the treatment of pancreatic endocrine tumors, the main issue is the prevention of liver metastasis, because once it takes place the prognosis is limited.<sup>7-14,38</sup> As already mentioned, Thompson *et al.*, have reported a good result with subtotal distal pancreatectomy and

enucleations of the pancreatic head cancer,<sup>24</sup> although surgeons at NIH had recommend local resection of pancreatic tumors larger than 2 or 3 cm, because the rate of liver metastasis is correlated with the size of the tumor.<sup>12,19,38</sup> As described above, Gibril *et al.*, also from NIH, reported recently that their strategy has brought about a high rate (23%) of development of liver metastasis during an 8-year observation period, which suggests that liver metastasis can take place no matter what the tumor size.<sup>26</sup> Lairmore and Piersall, who performed prospective genetic testing on large numbers of MEN-1 families, also suggested that in a subset of these patients, gastropancreatic endocrine tumors metastasize to the liver or distant sites more rapidly than expected; they believe that in the near future genetic testing will contribute to early detection of these rapidly growing tumors.<sup>15</sup> Until then, subtotal distal pancreatectomy should be applied more often for preventing liver metastasis from the numerous microscopic pancreatic tumors.<sup>24,37</sup> Total pancreatectomy seems to be too invasive, and has been rarely indicated; in the future, genetic testing might suggest the earlier necessity of partial or total pancreatectomy in selected patients.<sup>15</sup> At present, strict periodical surveillance of the growth pattern of the pancreatic tumors every 4 or 6 months with MRI is recommended after the curative resection of the duodenal gastrinomas.<sup>41</sup>

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