

A Prospective Study of Intraoperative Methods to Diagnose and Resect Duodenal Gastrinomas

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Objective

This study determined, prospectively, whether duodenotomy (DX) should be routinely performed in explorations for patients with Zollinger-Ellison syndrome (ZES).

Summary Background Data

Duodenal gastrinomas are now being found with increasing frequency in patients with Zollinger-Ellison syndrome. The surgical approach used to detect these tumors is controversial. Some recommend intraoperative endoscopy with transillumination (IOE) at surgery, while others recommend routine DX.

Methods

Beginning in 1989, the authors prospectively compared the ability of palpation, intraoperative ultrasound (IOUS), IOE, and DX (in that sequence) to detect gastrinomas in 35 consecutive patients with ZES. Each patient also underwent preoperative localization studies.

Results

Thirty-three of 35 patients (94%) had tumor detected and excised; duodenal gastrinomas were excised in 27 patients (77%). The average size of the duodenal tumors was 0.8 cm, significantly smaller ($p < 0.005$) than the pancreatic and lymph node tumors in this series. Standard palpation after a Kocher maneuver identified 19 of the 31 duodenal tumors (61%) in the 27 patients. IOUS revealed only eight duodenal tumors (26%) and no new lesions. IOE identified 20 duodenal gastrinomas (64%) and 6 new lesions. DX identified 31 duodenal tumors (100%) and 5 additional tumors. The morbidity rate was 17%. One patient had a duodenal fistula after operation (2.8%) and subsequently recovered. No patient died.

Conclusions

These results demonstrate that the duodenum is the most common location for gastrinoma in patients with ZES (77%) and that DX to detect and remove duodenal gastrinomas should be routinely performed in all explorations for patients with ZES.

The Zollinger-Ellison syndrome (ZES) was first described in 1955 as severe peptic ulcers and high gastric acid output associated with pancreatic islet cell tumors now known to produce gastrin.¹ The first ulcerogenic duodenal tumors were described in 1958 by Oberhelman et al.² Since then, many studies³⁻⁵ have shown that the duodenum is an important site for gastrinomas (from 6% to 43% of all gastrinomas that are identified appear there).⁶⁻⁹

Despite improvements in preoperative imaging and localization studies, and heightened awareness of the anatomic distribution of gastrinomas,⁶ the long-term cure rates for sporadic ZES have only increased to 30% to 40%,^{8,10} except for one recent report of 82%.⁴ This may be due to failure to identify small duodenal gastrinomas, which frequently are not seen on preoperative imaging studies^{5,8,11} and may also be missed at surgery. Several reports have shown that occult tumors in the resected duodenum were discovered incidentally by the pathologist in 16% to 33% of cases.^{7,12,13} Therefore, developing better methods to localize small duodenal tumors may be one of the most important factors to improve the cure rate for patients with sporadic ZES.

In the last few years, a number of techniques have been proposed that may help localize small duodenal gastrinomas; these include routine duodenotomy (DX), intraoperative endoscopy with transillumination (IOE), intraoperative ultrasound (IOUS), and endoscopic ultrasound.^{3,12-17} In a prospective study, IOUS was shown to be relatively insensitive for duodenal wall tumors,¹⁶ and the experience with endoscopic ultrasound is too limited to be assessed now. The risks and benefits of routine DX to search for occult gastrinomas have been debated.^{3,14,15} Some authors advocate DX,³ while others perform DX only if no tumor is found after a careful exploration.⁴ We originally proposed the routine use of IOE and have previously demonstrated that it was better than standard palpation to identify duodenal gastrinomas.¹⁵ However, because of the dramatic results obtained by Thompson et al. with DX in a few patients,³ the inability of IOE to rule out medial wall duodenal gastrinomas, and the possibility that routine DX might increase the complication rate in patients with ZES, in 1989 we developed a clinical protocol to systematically evaluate the available intraoperative methods for detecting duodenal gastrinomas. We compared standard palpation, IOUS, IOE, and DX (in that sequence) in 35 consecutive patients with ZES. Pathologic proof of gastrinoma was used to judge the utility of the intraoperative methods.

MATERIALS AND METHODS

Since 1989, 35 consecutive patients with ZES have undergone exploration for gastrinomas and have had the following diagnostic maneuvers performed sequentially during surgery: (1) palpation, (2) IOUS, (3) IOE, and (4) DX. Preoperative laboratory testing for the diagnosis of ZES and imaging were performed as described previously.^{5,8}

Surgery was performed according to a previously described protocol.⁸ Upon entering the peritoneal cavity, the liver, stomach, duodenum, small bowel, mesentery, pancreas, pelvis, and retroperitoneal regions in the upper abdomen are explored. An extended Kocher maneuver mobilizes the duodenum and pancreatic head. The pancreatic body and tail are approached through the lesser sac by opening the gastrocolic ligament, and the splenic flexure is mobilized to better expose the tail. The mobilized duodenum, pancreatic head, body, and tail are carefully palpated (Fig. 1A). Ultrasound imaging with a 10-MHz real-time transducer is then performed on the same areas as described previously and as shown in Figure 1B.¹⁶ The extensive mobilization is essential for optimal detection of tumors for both palpation and IOUS. Suspicious areas in the liver are also imaged and biopsied, as indicated. As described previously,¹⁵ IOE is done by inserting an upper gastrointestinal endoscope orally and advancing it into the duodenum. Lesions not transilluminated (Fig. 2A) are identified and examined further during the DX. A lesion may also be identified as a submucosal mass by the endoscopist. It is often helpful to mark the lesion with suture to identify it upon opening the duodenum (Fig. 3). If there are duodenal lesions already identified by palpation, ultrasound, or IOE, the DX is designed to encompass these lesions (Fig. 2B). If there are no lesions identified, a modest longitudinal incision (approximately 3 cm) is made in the anterolateral surface of the duodenum centered on the second portion (Fig. 4A), and the entire duodenal wall is palpated carefully. Suspicious lesions or nodules on the medial wall are not excised until a catheter is passed through the

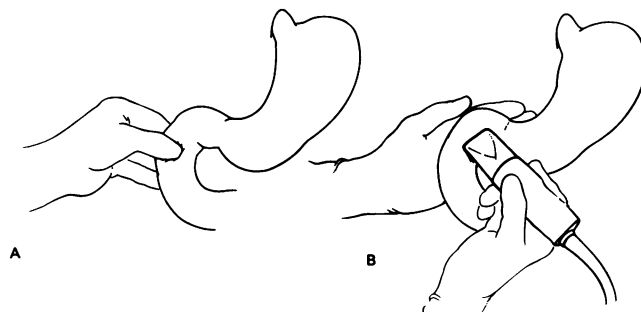


Figure 1. (A) Palpation of duodenum between thumb and forefinger. (B) IOUS of duodenum with 10-MHz real-time transducer.

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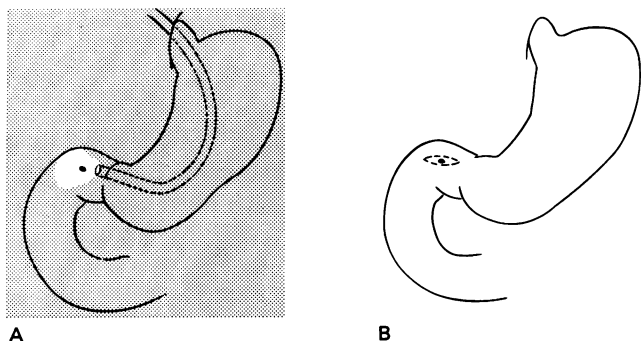


Figure 2. (A) Transillumination of gastrinoma in first portion of duodenum by IOE. (B) Location of duodenotomy guided by identification of tumor by transillumination.

common bile duct into the duodenum to identify the ampulla of Vater. Suspicious lesions found in the bowel wall are excised with a full-thickness rim of normal tissue and sent for pathologic analysis. Lymph nodes from the peri-pancreatic head, common bile duct area, and celiac axis are routinely excised and/or sampled. Other lesions found in the pancreas and liver are excised as previously described.^{5,8} The duodenum is closed in two layers transversely, if possible, to minimize the risk of leakage and obstruction (Fig. 4B). If this is not possible, a longitudinal closure is performed (Fig. 4B)

RESULTS

Patient Characteristics and Preoperative Imaging Studies

The characteristics and biochemical data of the 35 consecutive patients who underwent the above detailed exploration for ZES are summarized in Table 1. Each pa-

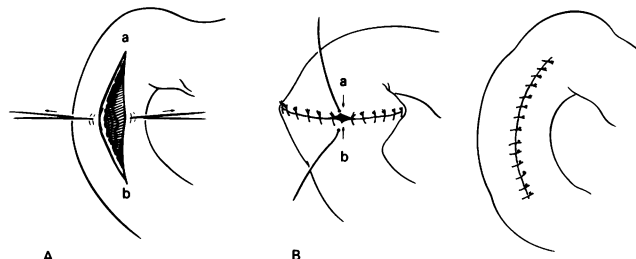


Figure 4. (A) Location of duodenotomy if no tumor was identified by other methods. (B) Transverse and longitudinal closure of duodenotomy.

tient had biochemical evidence of ZES (Table 1). There were 24 men and 11 women (average age at surgery, 48 years; age range, 28 to 69 years). Five patients had multiple endocrine neoplasia syndrome type 1 (MEN-1). The average time from the onset of symptoms to surgical exploration was 8.4 years (range, 0.6 to 35.2 years). The average time from diagnosis to surgery was 2.3 years (range, 0.3 to 22.6 years). Four patients had previous ulcer surgery; three had perforated ulcers oversewn and one had a vagotomy with Billroth II reconstruction. Of note, this patient did not undergo IOE because of technical difficulty in negotiating the Billroth II reconstruction. Three patients were previously explored for gastrinoma. One patient had an initial negative exploration and was found to have a liver metastasis but no primary tumor at her second surgery. Another patient initially had a pancreatic head tumor excised and then had two duodenal wall tumors and a lymph node tumor removed at his second operation. The third patient had a peripan-

Table 1. PATIENT CHARACTERISTICS (n = 35)

Characteristic	
Age at surgery (yr)	
Mean	48
Range	28-69
Sex (M/F)	24/11
MEN-1 (present/absent)	5/30
Time from symptoms to surgery (yr)	
Mean	8.4
Range	0.6-35.2
Time from diagnosis to surgery (yr)	
Mean	2.3
Range	0.3-22.6
Basal acid output (mEq/hr)	
Mean	39.5
Range	10.5-95.0
Fasting gastrin (pg/ml)	
Mean	746
Range	144-4660
Secretin stimulation test (% pos)	88
Prior ulcer surgery (no. of patients)	4



Figure 3. Two-mm duodenal gastrinoma identified by transillumination. Note the suture placed for easier identification when the duodenum is opened.

Table 2. TUMOR LOCATION AND SIZE

	Location				Total*
	Duodenum	Lymph Node	Pancreas	Liver	
No. of patients	27	19	4	3	35
No. of lesions	31	24	5	4	64
Size in cm (range)	0.8 (0.2–2.0)†	2.1 (0.4–5.0)	2.7 (0.7–5.0)	2.2 (0.3–7.0)	1.96 (0.2–7.0)

* A total of 64 tumors were found in 35 patients. No tumor was found in two patients.

† $p < 0.005$ comparing the size of duodenal vs. lymph node and pancreas tumors (Wilcoxon rank-sum test).

creatic lymph node removed at her first operation and subsequently had a duodenal tumor and two small liver metastases excised 1 year later.

Preoperative radiographic localization studies were performed on each patient. Considering only the patients with duodenal tumors ($n = 27$), imaging studies consisting of ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and selective angiography identified tumor in 14 of 27 patients (52%). Transhepatic portal venous sampling for gastrin localized tumor to the pancreatic head and duodenal areas in 17 of 22 patients (77%), and selective arterial secretin injection with hepatic vein gastrin measurements localized gastrinoma similarly in 22 of 23 patients (96%).

Tumor Location and Size

Sixty-four tumors were found in the 35 patients. No tumors were found in two patients. Focusing on duodenal tumors, 27 patients (77%) had 31 tumors. Three patients had multiple duodenal tumors—two patients had two tumors and one patient had three. Only one of these three patients had MEN-1. The sizes of the tumors ranged from 0.2 to 2 cm (average size, 0.8 cm). Associated with duodenal tumors, 14 patients (52%) had positive lymph nodes, 4 patients (14%) had pancreatic tumors (3 patients had MEN-1), and 1 patient (4%) had a liver metastasis. Data for tumors at other locations are summarized in Table 2. The size of duodenal tumors is

significantly smaller ($p < 0.005$, Wilcoxon rank-sum test) than the size of tumors found in the lymph nodes and pancreas.

Intraoperative Detection of Tumors

Each intraoperative method had high specificity and positive predictive value in detecting gastrinomas in various areas (Tables 3 and 4). Palpation had an overall sensitivity of 67%, and a negative predictive value (NPV) of 25%. This method was particularly effective in finding pancreas and liver lesions. IOUS had an overall sensitivity of 48%, and an NPV of 18%. It had the highest sensitivity for pancreatic lesions, and was able to identify a positive lymph node not found by palpation. The low NPV for both studies indicates that a negative finding is not reliable.

The results for duodenal tumors of intraoperative palpation, IOUS, IOE, and DX are presented in Tables 3 and 4 and Figure 5. Palpation detected 20 lesions—19 were identified pathologically as gastrinomas and 1 lesion was found to be a duodenal lipoma. The sensitivity and specificity were 61% and 95%, respectively. The sizes of tumors detected by this method ranged from 0.5 to 2.0 cm (average size, of 1.0 cm). IOUS detected eight lesions for a sensitivity and specificity of 26% and 100%, respectively. It did not identify any new lesions. IOE detected six new lesions not found on palpation and ultrasound. Overall, it detected 22 lesions, 2 of which were false-posi-

Table 3. SIZE AND INTRAOPERATIVE DETECTION OF DUODENAL TUMORS*

Method	Size in cm (Range)	No. of Lesions Detected					No. of New Tumors Found
			TP	FP	FN	TN	
Palpation	0.98 (0.5–2.0)	20	19	1	9	7	19
IOUS	0.88 (0.5–1.5)	8	8	0	20	7	0
IOE	0.77 (0.2–2.0)	22	20	2	9	7	7
Duodenotomy	0.80 (0.2–2.0)	34	31	3	0	7	5

TP: true-positive; FP: false-positive; FN: false-negative; TN: true-negative.

* A total of 31 duodenal tumors were found in 27 patients.

Table 4. INTRAOPERATIVE DETECTION OF TUMORS

Method	Sensitivity/Specificity by Location of Tumor					PPV	NPV
	Duodenum	Lymph Node	Pancreas	Liver	Overall		
Palpation	0.61/0.95	0.65/1.00	1.00/1.00	1.00/1.00	0.67/0.99	0.97	0.25
IOUS	0.26/1.00	0.61/1.00	0.80/1.00	0.50/1.00	0.48/1.00	1.00	0.18
IOE	0.64/0.91	N/A	N/A	N/A	0.64/0.90	0.91	0.39
Duodenotomy	1.00/0.91	N/A	N/A	N/A	1.00/0.90	0.90	1.00

PPV: positive predictive value; NPV: negative predictive value; N/A: not applicable.

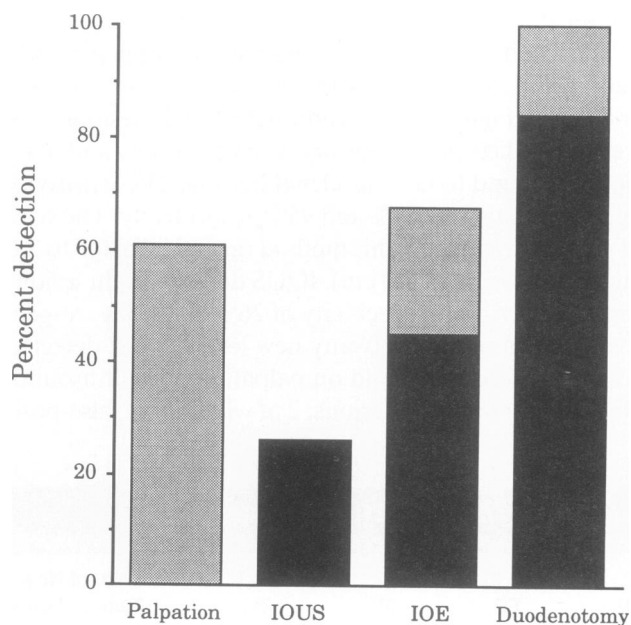
tives (sens/spec = 64%/91%). One of the false-positives was the previously mentioned lipoma, and the other was the accessory pancreatic duct. The sizes of tumors detected by this method ranged from 0.2 to 2.0 cm (average size, 0.77 cm). An example of the utility of IOE is seen in a 51-year-old man with sporadic ZES (Fig. 6). A 1-cm tumor was palpable in the first part of the duodenum. IOUS confirmed the palpable tumor. On IOE, two additional tiny tumors (0.2 and 0.5 cm) were seen in the second part. This enabled a directed DX to encompass all three tumors in one specimen (Fig. 6). DX identified five new tumors not found by palpation, IOUS, or IOE (Fig. 5). The sensitivity and specificity was 100% and 91%, respectively. There were three false-positives—the lipoma, accessory pancreatic duct, and a nodule identi-

fied as normal duodenum pathologically. The sizes of tumors detected by this method ranged from 0.2 to 2.0 cm (average size, 0.80 cm).

Figure 7 illustrates the size and position of the duodenal tumors found by palpation, IOE, and DX. Sixteen tumors were found in the first part of the duodenum (D1), 10 in the second part (D2), and 5 in the third part (D3). Of the seven new lesions found by IOE, 3 were in D1, 2 in D2, and 2 in D3. Of the five new lesions found by duodenotomy, 3 were in D1 and 2 were in the medial wall of D2. The sizes of these lesions discovered by IOE or DX were not significantly different from those of the duodenal tumors found by palpation.

Postoperative Complications

Six of 35 patients (17%) had postoperative complications (Table 5). Several patients had more than one complication. There were no deaths. Two patients (5.7%)



Intraoperative method

Figure 5. Intraoperative detection of duodenal tumors. The shaded areas represent the per cent of new lesions found by each method. The black areas represent the per cent of lesions also found by other methods.



Figure 6. Pathology specimen of multiple duodenal tumors with scale in centimeters. The large lesion (right side of figure) was identified by palpation and the two smaller lesions (left side of figure) were found on transillumination, which helped to guide the placement of this large duodenal excision. The duodenotomy closure was longitudinal (see Fig. 4B) in this case.

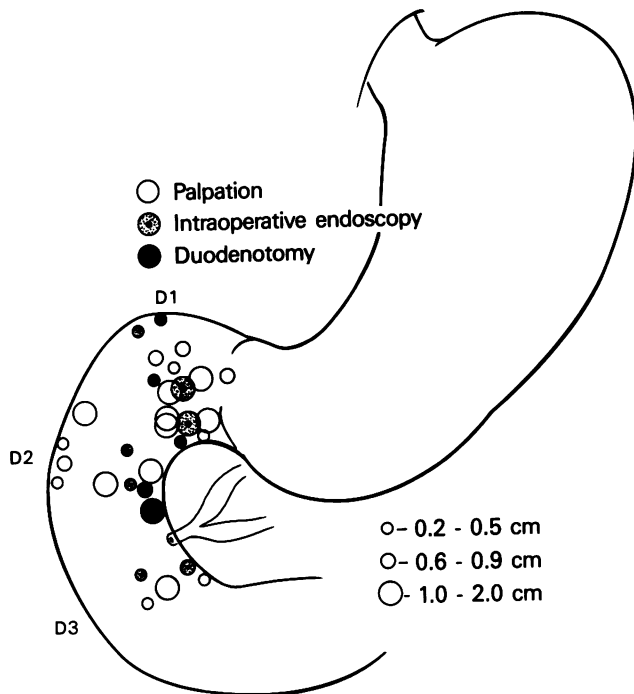


Figure 7. Schematic representation of size and location of duodenal tumors found by different methods. Tumors are represented by size and method detected (see key on figure) and are depicted in general area found (i.e., D₁ vs. D₂, medial vs. lateral). D₁, D₂, and D₃ refer to first, second, and third portions of the duodenum, respectively.

had clinically significant pancreatitis, defined as symptomatic hyperamylasemia that prolonged recovery. Of note, one patient had pancreatitis caused by intraoperative injury of the pancreatic duct by biopsy of the accessory pancreatic duct, which appeared suspicious for a gastrinoma on IOE as well as at DX. The other patient had pancreatitis associated with duodenal leak, and intra-abdominal abscesses. This patient had a previous vagotomy and Billroth II reconstruction for ulcer disease. The gastrinoma was found by palpation in the medial wall of the second part of the duodenum, embedded in thick scar tissue from prior surgery and/or ulcer disease. The wide excision of the abnormal duodenal wall as well as possible devascularization from prior surgery may have contributed to the duodenal leak and subsequent abscess and pancreatitis. The remaining patient, who had an intra-abdominal abscess, did not have evidence for duodenal leak on several contrast radiographic studies, nor at laparotomy to drain this abscess. However, she suffered gait disturbance from aminoglycoside toxicity after operation. One patient (2.8%) had a drain tract infection after enucleation of a pancreatic bed tumor. One patient underwent a subsequent operation for a small bowel obstruction, but no anatomic obstruction was found. One patient had a wound infection, and the

resulting fascial dehiscence was repaired during operation.

DISCUSSION

This consecutive series of 35 patients underwent a prospectively determined, systematic sequence of intraoperative maneuvers to determine the best method for finding gastrinomas, especially small lesions in the duodenum.

Preoperative imaging studies (US, CT, and MRI) were poor at localizing duodenal tumors (sensitivity = 15%). Arteriography alone had a higher sensitivity, but still missed 63% of the duodenal tumors. Functional localizing studies such as transhepatic portal venous sampling for gastrin and selective arterial secretin injection with hepatic vein gastrin measurements had high sensitivities (77% and 96%, respectively), but were only specific to the region of the pancreatic head and duodenum. Thus, in most cases it remains the surgeon's task to find the tumor within the pancreatic head and/or duodenum.

In this series including both sporadic and MEN-1 cases, gastrinomas were identified in 33 of 35 patients (94%) and duodenal gastrinomas were found in 27 of 35 patients (77%). Previously published reports^{4,6,7} have a lower tumor detection rate, especially within the duodenum. This difference may be due to the small size of many duodenal gastrinomas. The duodenal tumors in our study had sizes ranging from 0.2 to 2.0 cm (average size, 0.8 cm), significantly smaller ($p < 0.005$) than the lymph node or pancreatic tumors. Therefore, it is likely that some small duodenal gastrinomas were missed in previous studies, especially if only palpation was done, which was usually the case. In our study, only 19 tumors (61%) were identified by palpation alone.

Previous studies have suggested IOUS may be helpful in finding gastrinomas, although a prospective study found it to be of limited value in localizing a small num-

Table 5. POSTOPERATIVE COMPLICATIONS

Type	No.	%
Pancreatitis	2/35	5.7
Duodenal leak	1/35	2.8
Intraabdominal abscess	2/35	5.7
Drain tract infection	1/35	2.8
Small bowel obstruction	1/35	2.8
Wound infection	1/35	2.8
Aminoglycoside ototoxicity	1/35	2.8
No. of patients with complications	6/35	17.1

ber of duodenal gastrinomas.¹⁶ Our results confirm this finding. IOUS failed to detect any duodenal lesions not found by palpation alone, but it was useful in identifying lymph nodes and pancreatic tumors not found by other methods. A recent study suggested IOE would identify additional duodenal tumors not found by palpation and/or IOUS.¹⁵ Our prospective study confirms this finding in that IOE found six new tumors (19%). Our study demonstrates, however, that the addition of IOE alone is not sufficiently sensitive to detect all duodenal gastrinomas because DX detected an additional five (16%) new tumors. These results confirm, in a prospective study, the value of routine DX proposed by Thompson et al.³ An additional reason for using routine DX was the detection of duodenal tumors in patients with multiple tumors that otherwise would have missed. Three patients in this series had multiple duodenal tumors. Some of these tumors were so small (0.2 cm) they could only be identified with IOE or careful palpation of the duodenal wall at DX. Another four patients had associated pancreatic tumors. Of these, two patients had duodenal tumors found only by DX. If routine DX was not performed, these two patients would still have tumor remaining after their explorations.

In this study, we were able to find duodenal tumors in a large proportion of patients (77%) without undue complications by using our systematic approach of palpation, IOE, and DX. Based on our results, routine DX should be performed on all patients undergoing exploration for gastrinoma. It is clearly superior to IOE for the identification of duodenal wall tumors. However, IOE identifies most duodenal gastrinomas and it directs placement of the DX so that multiple or excessively long incisions in the duodenum are avoided. The short length of follow-up in this series of patients does not allow any conclusion about cure rates or prevention of metastasis with this approach. Because duodenal gastrinomas are shown to be malignant in 54% to 75% of cases^{11,12,18} and the prognosis for patients with extensive metastatic disease is poor (20% survival rate at 5 years),¹⁹ we believe that systematic identification and removal of all tumors, which can only be done with routine DX, may result in prolonged survival and increase cure rates for patients with ZES.

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