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Invited Commentary

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Recent studies have shown that the duodenum is a more common site of primary gastrinomas than previously thought. It is currently estimated that 30% to 50% of patients with sporadic Zollinger-Ellison Syndrome (ZES) have duodenal tumors [1–4]. Furthermore, the majority of multiple endocrine neoplasia type I (MEN-I) patients with ZES have one or more duodenal tumors with or without additional gastrinomas or other neuroendocrine tumors [5–9]. It also may be surmised that the majority of patients who have been explored with biochemical evidence of ZES, but negative findings of gastrinoma at exploration, have microgastrinomas of the duodenum [10]. Finally, there is accumulating evidence that the "lymph node gastrinoma" represents a metastasis from an occult duodenal primary tumor which may still be present or previously removed and undetected after a partial or total gastrectomy [1, 4, 11–13]. Thus, it is apparent that an awareness of the frequency of duodenal gastrinomas and an ability to detect them at exploration is of critical importance in improving the cure rate of patients with ZES who present without liver metastases.

Imamura and colleagues found that only 21 of 114 patients proven to have ZES in Japan from 1980 to 1991 had duodenal primary tumors whereas 49 gastrinomas arose from the pancreas. However, 32 (28%) explorations for ZES were negative. If most of these were microgastrinomas of the duodenum, the incidence of such tumors in potentially curable cases is nearly 50%.

Our experience during the past decade in exploring patients with ZES who had no apparent liver metastases, has shown that approximately half of them had either a duodenal gastrinoma or lymph node metastasis [4, 8–10]. In those patients with only a lymph node source of gastrin found, a previous partial or total gastrectomy had been done.

The authors observation that duodenal gastrinomas are less biologically aggressive than gastrinomas of pancreatic origin is consistent with those of a number of other surgeons since the original favorable results after surgical excision and long-term follow-up of a group of 11 patients reported by Oberhelman in 1972 [14]. He concluded that patients with duodenal gastrinomas, even with metastatic lymph node involvement, could be cured if the primary tumor and all metastatic nodes were removed. None of his surgically treated patients subsequently developed liver metastases. The present authors found that only 1 (9%) of 21 patients with a duodenal gastrinoma had liver metastases whereas 57% of those with pancreatic gastrinomas had liver involvement at the time of first presentation. The reported incidence of liver metastases in large series of ZES patients in the United States has shown a progressive decline from 60% to around 20–30% during the past two decades [13, 15, 16]. Whether this represents earlier diagnosis of the disease because of the widespread availability and use of gastrin assays is not clear, but likely. The occurrence of liver metastases in our own patients with duodenal gastrinomas has been similar to the authors in that only one of 17 recent patients presented with a liver metastasis. Furthermore, that patient had only a single large (12 cm) metastasis in the right lobe. He underwent a right lobectomy, excision of the primary tumor plus 9 metastatic lymph nodes and after more than one year has maintained a normal basal and secretin stimulated gastrin level. Unlike the authors, we have not found any sporadic duodenal gastrinomas that were either multiple or in association with a concomitant pancreatic gastrinoma, nor have any similar cases been previously reported (Kyoto, Cases 1,2) [4–6]. Because these are common findings in MEN-I patients, one wonders whether these patients had a full endocrine evaluation for other components of the syndrome.

The treatment of duodenal gastrinomas is controversial. In the authors personal experience with 7 patients in Kyoto, 6 were treated by Whipple procedures with one death three months postoperatively from heart failure. In the total Japanese series, an additional 4 patients had Whipple procedures and 13 patients had local excisions with or without gastrectomy. We have favored enucleation of tumors <0.5 cm in diameter and excision with a margin of full thickness duodenal wall for larger neoplasms. In all cases, regional dissections of peripancreatic and hepatoduodenal lymph nodes is required because even tumors as small as 1–2 mm have been associated with proven metastases [4, 9, 10]. More than 60% of our patients with

microgastrinomas have had proven lymph node metastases. With the exclusion of one patient with MEN-I, all of our patients treated during the past 10 years have normal gastrin levels and only one has required a "second look" procedure to excise an overlooked metastatic lymph node in the hepatoduodenal ligament. Our results suggest that a more conservative approach can be successful in both sporadic and MEN-I patients providing all involved nodes are excised as well as one or more primary tumors without incurring the potential morbidity and mortality of a pancreatic duodenotomy.

We are in agreement with the authors that the cellular origin of duodenal gastrinomas differs from that of pancreatic gastrinomas with resultant differences in both biological behavior and immunohistological findings. None of 11 of our recently studied duodenal gastrinoma stained for either insulin or glucagon but all stained positive for gastrin. All of them demonstrated mRNA for gastrin, chromogranin, and neuronspecific enolase, whereas none showed mRNA for proopiomelanocortin (POMC) or ACTH using *in situ* hybridization techniques. Both mRNA, POMC, and ACTH have been found in 30% of our malignant pancreatic gastrinomas and their presence appears to be an indication of aggressive biological behavior [17].

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