Surgery for Gastrinoma and Insulinoma in Multiple Endocrine Neoplasia Type 1

Jeffrey A. Norton, MD,* Tony D. Fang, MD,* and Robert T. Jensen, MD,† *Stanford, California, and Bethesda, Maryland*

Key Words

Pancreatic endocrine tumor, endocrine neoplasia type 1, gastrinoma, insulinoma

Abstract

The surgical management of pancreatic endocrine tumors in patients with multiple endocrine neoplasia type 1 remains controversial. Gastrinoma and insulinoma are the 2 most common functional pancreatic neuroendocrine tumors in patients with multiple endocrine neoplasia type 1. Gastrinomas cause gastric acid hypersecretion and peptic ulcer disease that are best managed using proton pump inhibitors. Surgery to remove the gastrinoma in patients with multiple endocrine neoplasia type 1 is seldom curative unless a more extensive Whipple pancreaticoduodenectomy is performed. Because the prognosis is excellent, aggressive resections such as a Whipple procedure are only indicated for large, locally metastatic, advanced tumors. Furthermore, surgery to remove imageable tumors that are 2 cm in diameter is associated with excellent outcomes and decreased probability of liver metastases. Because gastrinomas are commonly multiple and most originate in the duodenum and develop lymph node metastases, the duodenum should be opened and all tumors and lymph nodes excised. Insulinomas cause hypoglycemia that results in neuroglycopenic symptoms. Medical management of the hypoglycemia is less effective than that of the gastric acid hypersecretion. Fortunately, the insulinoma is usually clearly identified using routine pancreatic imaging studies. There is a high likelihood of cure when the insulinoma is excised surgically. However, recurrent hypoglycemia may occur, and careful follow-up is indicated. (*JNCCN* 2006;4:148–153)

From the *Department of Surgery, Stanford University Medical Center, Stanford, California, and †Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland.

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Correspondence: Jeffrey A. Norton, MD, Stanford University Medical Center, Department of Surgery, Room H-3591, 300 Pasteur Drive, Stanford, CA 94305-5641. E-mail: janorton@stanford.edu

The gene responsible for multiple endocrine neoplasia type 1 (MEN1) was identified recently.¹ MEN1 is diagnosed clinically in patients who have tumors in at least 2 of the following tissues: parathyroid, endocrine pancreas, and pituitary. A simple diagnostic criterion of MEN1 is a cluster of at least 2 first-degree relatives, one with a clinical diagnosis of MEN1 and the other with at least one of the endocrine tumors associated with MEN1.²

Gastrinomas (neuroendocrine tumors that secrete gastrin and cause Zollinger-Ellison syndrome [ZES]) are the most common functional neuroendocrine tumors in MEN1,³ and management of gastrinoma in patients with MEN1 has been controversial.⁴ Approximately 50% of patients with MEN1 develop gastrinoma by the age of 50 years.² Gastrinomas are often multiple, originate in the duodenum, and are metastatic to adjacent lymph nodes at diagnosis; approximately 15% show aggressive growth. Medical management of the excessive gastric acid secretion, peptic ulcer disease, and diarrhea using proton pump inhibitors is very effective. The usual doses for MEN1 are twice the standard dose for peptic ulcers, given twice daily.

Studies of the effect of surgery on gastrinoma in patients with MEN1 show that it is seldom curative but can control malignant tumors and prevent liver metastases. Surgery is recommended when patients have identifiable, large (2 cm in diameter) tumors that may be malignant.

Insulinoma with associated hypoglycemia is the second most common functional pancreatic neuroendocrine tumor in MEN1. Between 10% and 35% of patients with MEN1 will develop insulinoma.² Insulinomas are commonly benign, easily identified within the pancreas on preoperative imaging, and usually not multiple. Because medical management of the hypoglycemia is seldom adequate, surgical resection is the best treatment for MEN1 insulinoma. This article details the technique, results, and rationale for different surgical procedures for patients with MEN1 who have gastrinoma or insulinoma.

Surgical Cure Rate in Patients with Zollinger-Ellison Syndrome and MEN1

It became clear 15 years ago that most gastrinomas in patients with MEN1 and ZES are located in the duodenum, not the pancreas.^{5,6} Previously, failure to identify the primary gastrinoma in the duodenum resulted in a low surgical cure rate,⁷⁻¹² and some researchers suggested that routine surgical exploration for cure of ZES in MEN1 patients should not be performed. Furthermore, more recent studies (Table 1) still indicate that surgical cure is very low (14%)¹³⁻¹⁹ unless a Whipple procedure (resection of the proximal pancreas and duodenum) is performed. The determination of cure requires measurement of fasting serum levels of gastrin, a secretin test that shows no increase in gastrin levels, and no tumor on postoperative imaging studies, including computed tomography (CT) and the more sensitive somatostatin receptor scintigraphy (SRS). A major criticism of the current literature is that most studies have inadequate testing and follow-up to document cure. In our experience,¹³ patients with MEN1 who initially appear to be cured can later experience recurrence. Recurrence is diagnosed when the secretin test shows an increase in gastrin levels before an elevated fasting serum level of gastrin or a tumor is detected on imaging studies.¹⁴ This inability to cure patients may be explained by incomplete resection of multiple small duodenal primary gastrinomas (Figure 1) and lymph node metastases.¹⁵ The surgeon may remove some of the tumors without identifying every tumor or lymph node. However, a Whipple procedure removes the entire gastrinoma triangle, including the pancreatic head, duodenum, and draining nodes.¹⁸ This procedure seems to have a higher cure rate but may also be associated with unacceptably high morbidity and mor-

Table 1 Surgical Cure Rate in 15 Series of Patients With MEN1 and ZES Treated With Local Resection Without Whipple Pancreaticoduodenectomy

Years	Patients, <i>N</i>	Cure Rate, <i>n</i> (%)
1990–2001	242	35 (14)

Source: Data are from Gibril et al.³

tality in patients with no symptoms and expected excellent survival.

Several small series have reported excellent results with the use of Whipple resection in patients with ZES and MEN1 (Table 2). In an apparently higher proportion of cases (88%) than with less extensive resection, Whipple pancreaticoduodenectomy has cured patients with ZES and MEN1. This finding suggests that Whipple resection increases cure rate in patients with ZES and MEN1.²⁰⁻²³ However, in each of these studies, serial secretin tests were not performed and recurrent ZES may have been missed. Certainly, Whipple resection is extensive and makes repeat surgery technically more difficult. These limitations are important for patients with ZES and MEN1 because patients with MEN1 may develop additional neuroendocrine tumors requiring additional surgery. Furthermore, if liver metastases develop after a Whipple resection, liver embolization cannot be used for treatment^{24,25} because of a high risk for ascending cholangitis and liver abscess. However, we believe that Whipple resection does have a role in select patients. It is recommended for younger patients with MEN1/ZES who have a large (> 3 cm) pancreatic head or duodenal tumor that cannot be enucleated

Figure 1 Multiple primary gastrinomas in the duodenum of a patient with multiple endocrine neoplasia type 1 (MEN1). (A) Surgical specimen shows 3 primary duodenal gastrinomas (*). (B) Microscopic examination shows a neuroendocrine tumor in the submucosa of the duodenum (dotted area).

of the parathyroid and pituitary disease is largely unknown. When patients die of metastatic neuroendocrine tumors,³⁸⁻⁴⁴ gastrinoma may or may not be the cause. Patients may also have another pancreatic neuroendocrine tumor or other malignant neuroendocrine tumors, such as a bronchial, thymic, or gastric carcinoid.^{43,44} However, some recent studies indicate that the gastrinoma and other pancreatic neuroendocrine tumors are the critical determinants of long-term survival.⁴⁵⁻⁴⁷

We believe this strongly indicates that imageable large pancreatic neuroendocrine tumors in patients with MEN1 should be removed surgically. This recommendation is based on results from numerous studies that show a strong correlation between primary tumor size and the development of liver metastases, which are the primary determinants of long-term survival in patients with pancreatic neuroendocrine tumors.^{27,33,38,48} Furthermore, 23% of these pancreatic neuroendocrine tumors have demonstrated aggressive growth and hepatic metastases.^{44,47} Nearly 40% of patients with aggressive neuroendocrine tumors die from tumor, which is greater than the mortality rate for patients with nonaggressive pancreatic neuroendocrine tumors. Most (50%–70%) patients with MEN1 and imageable neuroendocrine tumors of the pancreas (2–3 cm) who underwent surgical exploration had lymph node but not liver metastases.⁴⁷ Some researchers have interpreted this finding as support for earlier exploration when tumors are smaller.^{13,29} However, we think the primary indication for exploration at that time is to avoid liver metastases. Fourth, in a recent study involving 81 patients²⁶ with MEN1/ZES, the 15-year survival rates were 100% in 25 patients without surgery when pancreatic neuroendocrine tumors were smaller than 2.5 cm; 100% in 17 patients with surgical resection of a single pancreatic neuroendocrine tumor that was less than 6 cm; and 89% in 31 patients with multiple tumors 2 cm or larger or a single tumor larger than 6 cm tumor (with surgery). Distal pancreatectomy was not routinely performed, which suggests it is not necessary.²⁶

Currently, the only reliable clinical marker that allows prediction of the aggressiveness of a pancreatic neuroendocrine tumor in a patient with ZES and MEN1 is tumor size.^{27,38,48} The most important variable that affects survival in patients with MEN1 and gastrinoma is liver metastases.^{27,38,48} Studies have shown that in gastrinomas and other pancreatic neuroendocrine tumors, primary tumor size is highly predictive of the development of liver metastases.^{27,38,48} Therefore, because patients with ZES/MEN1 are seldom cured by surgery, patients with tumors 2 cm or smaller have a 100% 15-year survival rate, and patients with larger tumors have an increased probability of developing liver metastases, we recommend surgical resection of imageable tumors that are 2 cm or greater. A distal pancreatectomy should not be routinely performed unless the imageable tumor is in the tail of the pancreas. Surgery should focus on removal of the imageable tumor. If the imageable tumor is in the head of the pancreas, enucleation is recommended, if technically feasible. This procedure may not be feasible when the tumor abuts the pancreatic duct or common bile duct. If the imageable tumor is in the tail, distal pancreatectomy is preferred because it decreases the complication of pancreatic duct leak.

In addition, the surgeon should open the duodenum in patients with ZES to identify and remove small duodenal gastrinomas (Figure 1). These are usually multiple and frequently spread to adjacent lymph nodes; the surgeon should perform extensive lymph node sampling around the head of the pancreas. If tumors in the pancreatic head area are very large and multiple localized lymph node metastases are present (Figure 2), the surgeon should perform a Whipple procedure. This approach should increase the probability of long-term survival because it reduces the likelihood of liver metastases.⁴⁹

Surgical Management of Insulinoma in MEN1

Insulinoma is the second most common functional pancreatic neuroendocrine tumor in patients with MEN1.⁵⁰ It occurs in approximately 10% to 35% of cases² and causes severe neuroglycopenic symptoms secondary to hypoglycemia. Unlike gastrinoma, the symptoms are poorly controlled medically, but, fortunately, successful surgical resection of insulinoma in patients with MEN1 usually leads to complete amelioration of the hypoglycemia.⁵⁰⁻⁵⁴ This result occurs despite the fact that

Table 3 Surgical Cure Rate in Patients with MEN1 and Insulinoma

Patients, N	CT-Imageable Insulinoma, n (%)	Cure Rate, n (%)	Recurrence, n (%) / (time to recurrence)
7	7 (100)	6 (86)	1 (14) / (5 y)

pathologic analyses of the resected pancreas from patients with MEN1 show that most have multicentric neuroendocrine tumors.⁵⁵ However, clinical studies suggest that in MEN1 insulinoma, patients have a dominant pancreatic neuroendocrine tumor that can be clearly identified on conventional imaging studies such as CT, magnetic resonance imaging, and endoscopic ultrasound (Figure 3).^{50–53} The tumor identified by imaging is most likely the insulin-secreting tumor, and the surgery should be designed to remove it. In studies of patients with MEN1 insulinoma,^{51,53,54} removal of a clearly identified tumor has resulted in complete amelioration of the hypoglycemia in nearly every patient (Table 3). These tumors have not been subtle and are usually approximately 2 to 3 cm in diameter (Figure 3). These features are different from sporadic insulinomas that are usually more occult and measure approximately 1 cm in diameter.⁵⁶ Surgery should focus on excision of the preoperatively identified tumor. If the tumor is in the head of the pancreas, enucleation is preferred over Whipple resection. Intraoperative ultrasound is used during the surgery to facilitate tumor identification and removal (Figure 3). If the tumor is identified in the pancreatic tail, distal

pancreatectomy is preferred. Our initial cure rate has been very high (100%), with recurrent hypoglycemia occurring in only 1 of 7 patients (14%). Thus, the clinical syndrome of insulinoma in patients with MEN1 is a clear indication for surgery, and the surgery has a high probability of success. In the rare patient who has an insulinoma with multiple small tumors throughout the pancreas on preoperative imaging studies, or for whom no tumor is seen on imaging, the surgeon should consider venous insulin sampling using either portal venous or hepatic vein sampling after selective intra-arterial calcium injections.^{51,56}

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Figure 3 Multiple endocrine neoplasia type 1 (MEN1) and a 2-cm insulinoma in the head of pancreas. This small tumor was treated by enucleation. Pancreatic computed tomography scans with 3-dimensional reconstruction show (A) axial arterial phase; (B) coronal reconstruction; and (C) sagittal reconstruction. (D) Intraoperative ultrasound. The black arrows indicate insulinoma. Abbreviations: PV, portal vein; SMV, superior mesenteric vein; CA, celiac axis; CHA, common hepatic artery; LHA, left hepatic artery; RHA, right hepatic artery.

Surgery in Multiple Endocrine Neoplasia Type 1

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