Islet Cell Tumors

The islet cells of the pancreas were originally described by Langerhans in 1869. They comprise approximately 1% to 2% of the pancreatic mass. Tumors arising from the islet cells are correspondingly uncommon among the roster of potential pancreatic tumors. Endocrine tumors arising from the pancreatic islet cells are rare entities, with a clinical incidence of 0.2 per 100,000 individuals.[1] These tumors account for 2% to 4% of clinically detected pancreatic neoplasms.[2] Neuroendocrine tumors of the pancreatic islet cells may be overtly functioning or exhibit no syndrome of endocrine excess in the patient. Functional islet cell tumors such as gastrinomas or insulinomas typically produce their polypeptide hormones such that the associated symptoms lead to the diagnosis of these tumors. Other tumors arising from the islet cells, however, do not produce overt symptoms and therefore patients harboring these tumors are more likely to present with large tumors or metastatic islet cell cancers. This monograph will detail the typical presentation associated with islet cell tumors, discuss the evaluation, and then detail the treatment of these tumors.

Epidemiology and Pathology

Neuroendocrine tumors have cells with abundant clear cytoplasm and uniform nuclei arranged typically in a trabecular pattern but often also have glandular or gland-like elements[3] (Fig 1). Electron microscopy demonstrates the endocrine nature of these tumors with many electron-dense secretory granules in the cytoplasm.[4] The best known markers of neuroendocrine cells are neuron-specific enolase (NSE) and chromogranin A.[5,6] NSE is present in the cytosol and not related to the secretory product of the tumor. Chromogranin A is associated with the secretory granules of many neuroendocrine tumors. In addition to these general markers, specific immunostaining for particular secreted peptides such as insulin or gastrin confirms the diagnosis. Classification of endocrine tumors of the pancreas has recently been revised. The initial classification

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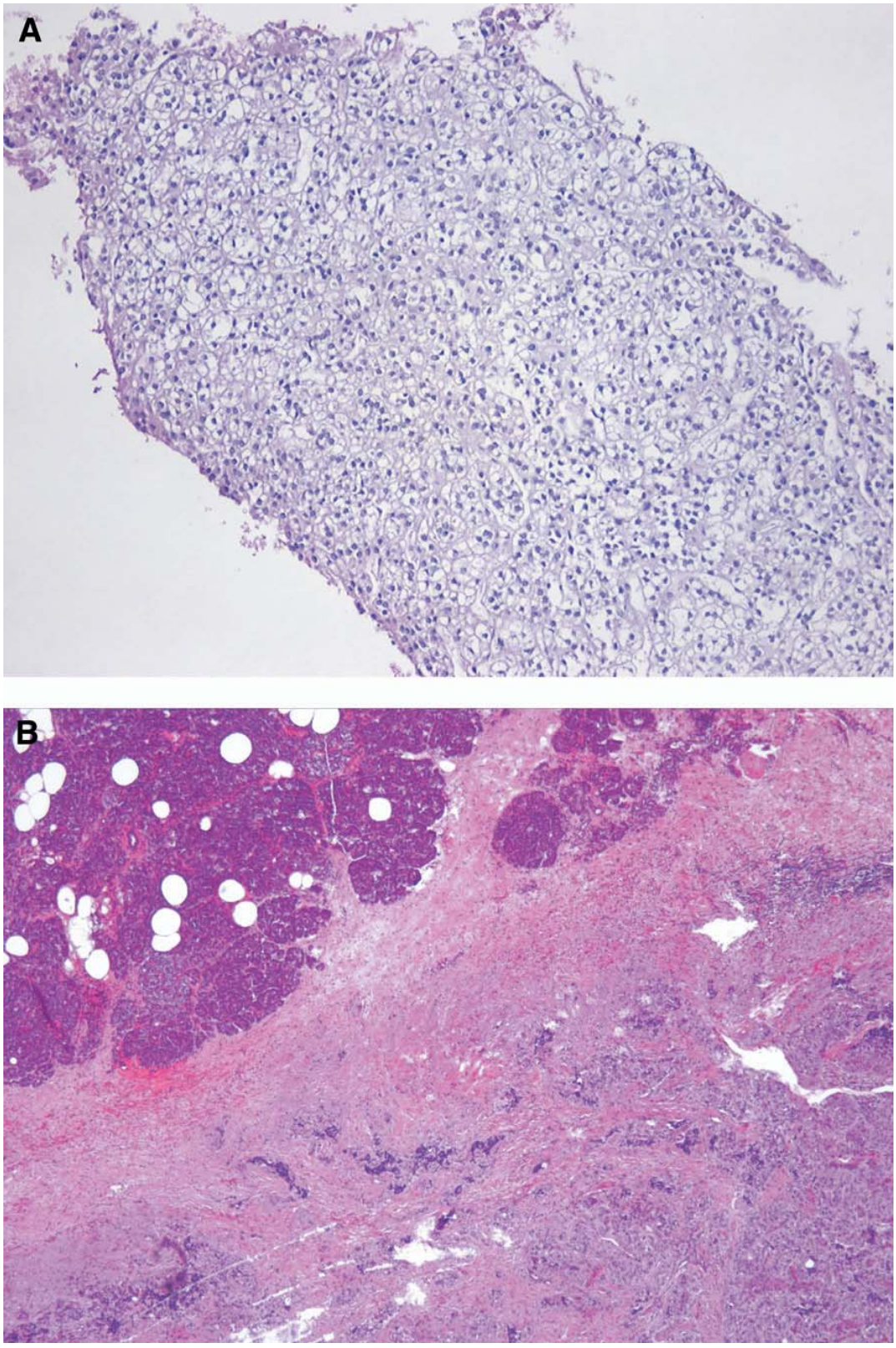

FIG 1. Microscopic appearance of a gastrinoma (A) and an insulinoma (B). (Color version of figure is available online.)

had depended on the degree of differentiation, the predominant cell type, and whether a clinical syndrome resulted. In 1995, Capella and colleagues proposed dividing these pancreatic endocrine tumors into categories based on whether they were functioning or nonfunctioning tumors of benign behavior, uncertain behavior, low-grade malignancy, or high-grade malignancy.[7] The latter assessment was based on the tumor size, the degree of local or vascular invasion, and the presence of metastases. This method of classification was validated by others[8] and later adopted by the World Health Organization.[9] In general, insulinomas are typically benign and unlikely to metastasize, but gastrinomas and glucagonomas are malignant with metastatic potential. In the absence of metastases, indicators of malignant potential are histopathologic demonstration of invasion into adjacent organs and vascular invasion. Unfortunately, these criteria and others such as architectural features, high mitotic index, nuclear pleomorphism, and capsular invasion may not be consistently reliable predictors of biologic behavior.[10,11] Other adjunctive tests have been reported. DNA ploidy may be helpful because an aneuploid pattern is associated with aggressive behavior in malignant pancreatic endocrine tumors, but DNA ploidy does not reliably distinguish benign from malignant tumors.[12,13] Immunohistochemistry showing increased staining for proliferating cell nuclear antigen or Ki-67 using a MIB-1 antibody has also been associated with malignant behavior and shortened survival.[14,15] In the study by Clarke and colleagues, a MIB-1 labeling index of greater than 10% was associated with a certainty of the development of metastases, but only 43% of patients with an index less than 10% developed metastases.

Functional Syndromes

Gastrinoma

In 1955, Zollinger and Ellison described 2 patients with a clinical triad of benign ulceration of the proximal jejunum, extreme acid hypersecretion, and a non-β islet cell tumors of the pancreas. The Zollinger-Ellison syndrome (ZES) is characterized by symptoms that are related to excess autonomous gastric acid secretion due to a neuroendocrine tumor. It was not until 1960, however, that the responsible peptide, gastrin, was first extracted by Gregory and colleagues. This neuroendocrine tumor, or gastrinoma, is most often identified in the duodenum and less commonly in the pancreas. The incidence of gastrinoma is approximately 0.2 to 2 per million population[16]and it occurs most frequently in the fifth decade of life.[17] At least 0.1% of patients with duodenal ulcer disease and

approximately 2% of patients with recurrent ulcers after appropriate medical therapy have a gastrinoma.[18,19] Approximately 60% of patients diagnosed with gastrinoma are men.[17] Seventy percent to 80% of gastrinomas occur sporadically and 20% to 30% occur as part of the multiple endocrine neoplasia type 1 syndrome (MEN1).[17,20]

Clinical Presentation. High serum gastrin levels in patients with a gastrinoma stimulate unregulated acid secretion from the gastric parietal cells. This, in turn, leads to a severe ulcer diathesis and injury to the small bowel mucosa, resulting in varying degrees of malabsorption. Epigastric pain and diarrhea are common presenting manifestations. Abdominal pain, when present, is due to ulcer disease and the diarrhea is due to the combination of acid hypersecretion and small bowel mucosal injury. In a large study of 261 patients with ZES, including 203 with sporadic disease, Roy and colleagues identified abdominal pain and diarrhea as the most common initial symptoms, present in 78% and 72% of patients, respectively.[17] Diarrhea is not typical of ulcer disease but is a prominent feature of ZES. In 7% to 13% of patients with ZES, diarrhea is the only presenting symptom.[21,22] Other common presenting symptoms included heartburn, nausea, vomiting, weight loss, and gastrointestinal bleeding. Ten percent of patients had only 1 symptom, most often abdominal pain, whereas 27% of patients presented with 2 symptoms, most often abdominal pain and diarrhea. The majority of patients, however, presented with 3 or more symptoms.[17] Other authors reporting smaller institutional or registry series have confirmed these common symptoms.[23-32]

At the time of presentation, peptic ulcer disease (PUD) confirmed by upper gastrointestinal contrast studies or endoscopy is present in more than 70% of patients. In addition to causing pain, the ulcers can bleed and, in a small percentage of patients, perforate.[17,21,22,30] Because ZES often manifests with abdominal pain similar to that seen in idiopathic PUD or with heartburn similar to that seen with gastroesophageal reflux, the proper diagnosis is frequently delayed. Patients presenting with these symptoms are frequently started empirically on antacid therapy, which helps alleviate symptoms associated with ZES. The mean duration of symptoms before diagnosis has been reported to range from 3.2 to 8.7 years.[17,24,27-31] Patients with diarrhea as a prominent symptom have been misdiagnosed as having Crohn's disease, irritable bowel syndrome, celiac sprue, lactose intolerance, infectious diarrhea, and idiopathic diarrhea.[17]

Because the diagnosis can only be made by maintaining a high index of suspicion, there are several clinical scenarios that should raise the suspicion for gastrinoma and prompt further evaluation. Included in these are ulcers in atypical locations such as the distal duodenum or jejunum,

multiple ulcers, PUD in the absence of *H. pylori* infection, ulcers that fail to respond to conventional treatment or that recur after cessation of medical treatment, PUD in association with diarrhea, persistent diarrhea without a clear etiology, family history of PUD, and PUD associated with hyperparathyroidism or other endocrinopathies. In an era of effective antacid therapy, some authors also advocate screening patients for ZES when complications of PUD occur, such as bleeding, perforation, or obstruction.[33,34]

The use of antacid therapy in patients with symptoms suggestive of PUD results in a less dramatic presentation and delay in diagnosis of ZES as well as more advanced disease at the time of eventual diagnosis. In a study reviewing the experience at Ohio State University, Ellison and Sparks[34] examined 108 patients with ZES during 4 time periods: 1955 to 1965 when the disease was first recognized, 1966 to 1975 when there was increased identification of gastrinoma, 1976 to 1985 when there was widespread application of the gastrin radioimmunoassay, and after 1986 when there was effective medical therapy. As expected, gastric surgery was less common in the fourth period. The incidence of metastatic disease was significantly lower in the third period than in the first 2 periods (19% versus 45% and 56%, respectively). Interestingly, in the fourth period, after antacid therapy became widely available, the incidence of metastatic disease increased to 55%. Similarly, the 5-year disease-free survival increased in the third period to 29% (versus 0% and 4% in the first and second periods, respectively) but decreased to 2% in the fourth period. The authors drew the conclusion that acid suppression therapy by histamine H_2-receptor antagonists (H_2-blockers) and proton pump inhibitors (PPI) is effective in relieving symptoms associated with ZES. However, with the availability of effective medical therapy, surgeons are seeing patients with more advanced disease and 5-year cure is less likely.[34] In a combined study from the Gastroenterology Unit in Rome, Italy, and the NIH in Bethesda, Maryland, Corleto and colleagues observed similar findings that suggested that widespread use of PPIs was masking and complicating the diagnosis of gastrinoma.[35] They found a highly significant decrease in the annual referral rates of patients with gastrinoma. They also identified an increase in the percentage of patients presenting with advanced disease. In addition, there was a decrease in the number of new diagnoses by 40% at both centers and a significant increase in the number of false positive diagnoses of gastrinoma. This increase in false positive diagnosis is due to the fact that chronic treatment with PPIs can increase gastrin levels in 80% to 90% of patients, thereby mimicking gastrinoma.[35,36]

TABLE 1. Differential diagnosis of elevated serum gastrin levels

Gastrinoma
Pernicious anemia
Renal failure
G cell hyperplasia
Atrophic gastritis
Retained or excluded antrum
Gastric outlet obstruction
Treatment with antisecretory agent

The diagnosis of a gastrinoma is made by measuring high serum gastrin levels.[37] A radioimmunoassay for gastrin was first described by McGuigan and Trudeau in 1968 and became available for use in the mid 1970s.[38] As indicated previously, the use of antisecretory agents can cause achlorhydria and an elevated fasting gastrin; therefore patients must discontinue the use of H_2-blockers or PPIs at least 48 hours before testing. A normal serum gastrin level is 100 to 200 pg/mL. A fasting serum level greater than 1000 pg/mL is diagnostic of gastrinoma. Levels this high are seen in approximately 30% of patients. Most patients with a gastrinoma, therefore, have more moderate elevations of fasting serum gastrin levels in the range of 200 to 1000 pg/mL.[33] In addition to a gastrinoma, other conditions exist that may be associated with an elevated gastrin level (Table 1). In equivocal cases when the serum gastrin level is greater than 200 pg/mL but less than 1000 pg/mL, a secretin stimulation test is necessary to establish the diagnosis of gastrinoma. Patients receive intravenous secretin (2 U/kg) after which serum gastrin levels are measured at 2-, 5-, 10-, 15-, and 30-minute intervals after secretin administration. A rise of more than 200 pg/mL confirms the diagnosis of a gastrinoma.

Some authors advocate also measuring basal and maximal gastric acid output since gastric acid hypersecretion is required for the diagnosis of gastrinoma. Tests for gastric acid production in ulcer disease establish the hypersecretion of acid and distinguish ZES from other causes of hypergastrinemia. Basal acid output (BAO) is greater than 15 mEq/h in patients without prior ulcer surgery and more than 5 mEq/h in patients who have undergone an acid-reducing operation such as an antrectomy and vagotomy. Some have suggested that a ratio of BAO to maximal acid output (MAO) in excess of 0.6 is a criterion for ZES, but 15% to 50% of patients with gastrinomas exhibit a BAO/MAO ratio of less than 0.6, so others argue that the ratio offers no diagnostic utility over measurement of BAO alone.[39] The most common other causes of increased fasting serum

concentrations[40] are seen in achlorhydria due to pernicious anemia or atrophic gastritis, so the measurement of acid production is a useful modality to diagnose ZES. Other causes of hypergastrinemia are antral G-cell hyperplasia, retained antrum after Billroth II gastrectomy, gastric outlet obstruction with distention, renal failure, and short gut syndrome. When the serum gastrin level is greater than 1000 pg/mL and the BAO is greater than 15 mEq/h, the diagnosis of ZES is established. Because up to 68% of patients with gastrinomas do not fulfill these criteria, when the gastrin level is mildly elevated (100 to 1000 pg/mL) and the gastric pH is less than 3, a secretin provocative test is needed to establish the diagnosis.[41] The most commonly used and recommended initial provocative test is the secretin stimulation test. Whereas gastrinoma patients have a rise in gastrin levels, patients with antral G-cell hyperplasia or retained antrum typically show a decrease or perhaps only a slight increase in gastrin levels.[42] Other provocative tests include calcium infusion or a 40-g protein meal test. Once a diagnosis of gastrinoma has been made, gastric acid hypersecretion is controlled with either an H_2-blocker or PPIs, and imaging studies are obtained to localize the lesion.

Anatomy and Tumor Biology. Gastrinomas were first reported to be non-beta-cell tumors in the pancreas; however, in most current series, most are duodenal in location outnumbering pancreatic gastrinomas 2:1 to 5:1.[20,43] Duodenal gastrinomas are usually smaller than 1.0 cm in diameter. They can be multiple and associated with lymph node metastases in 40% to 70% and hepatic metastases in 5% of patients.[20,44-52] Of duodenal gastrinomas, 58% are present in the first portion, 32% in the second, and less than 10% in the third or fourth portions of the duodenum.[43] For pancreatic primaries, they are most often identified in the head of the gland. The majority of gastrinomas are therefore identified within the gastrinoma triangle, an anatomic area bounded by the junction of the body and neck of the pancreas medially, the junction of the second and third portion of the duodenum inferiorly, and the junction of the cystic duct and common bile duct superiorly. In a large series from the National Institutes of Health (NIH) with 123 patients with sporadic gastrinomas, 47% of the primary tumors were located in the duodenum, 14% in the pancreas, 13% in a lymph node, and the remainder were found in other locations including the liver, bile duct, stomach, spleen, mesentery, and ovary.[20] Several studies have confirmed the presence of gastrinomas outside of the gastrinoma triangle.[23,53,54]

The biologic behavior of gastrinomas is variable. Studies have shown that there are aggressive and nonaggressive forms of gastrinoma, with the

aggressive form occurring in approximately 25% of patients.[50,55] The aggressive form is more common in women and in patients without MEN1. It has a shorter duration of disease, higher serum gastrin levels, and is associated with large pancreatic tumors and liver metastases. The long-term survival rate for patients with the aggressive form of gastrinoma is 30% compared with 96% for the nonaggressive form.[50,55] Several authors have attempted to elucidate the molecular pathogenesis of gastrinomas and to correlate identified genetic alterations with tumor invasiveness. Recent studies have shown that alterations in 2 tumor suppressor genes, the MEN1 gene on chromosome 11q13 and the p16INK4a gene on chromosome 9p21, are frequent in pancreatic endocrine tumors but these mutations are not predictive of tumor aggressiveness.[56-59] The oncogene HER2/*neu* has also been investigated but overexpression of HER2/*neu* does not appear to play a role in the molecular pathogenesis of most gastrinomas. There may be, however, a subset of patients in whom overexpression is associated with a more aggressive course.[60] Epidermal growth factor and hepatocyte growth factor have been found to be universally expressed in gastrinomas and overexpression was identified in approximately 15% of gastrinomas; this was found to correlate with increased growth and a lower rate of cure.[61] Additional studies are required before such markers will have the clinical utility to impact on the treatment of patients with gastrinoma.

With respect to prognostic factors, the presence of hepatic metastases conveys the worst prognosis. Similar to the distinction between aggressive from nonaggressive primary gastrinomas, there appears to be a subset of patients with liver metastases that progress rapidly. Sutliff and colleagues investigated 19 patients with liver metastases and found that 26% demonstrated no growth, 32% had slow growth, and 42% had rapid growth.[62] In patients with rapid growth, 62% died, whereas no patient with stable disease or slow growth of their tumors died from their disease. Again, further study into the molecular pathogenesis of liver metastases must be undertaken to identify biologic factors that can be used to guide clinical decision-making in the care of patients with metastatic disease.

Tumor Imaging. In more than 80% of patients, the primary tumor is found in the gastrinoma triangle, but because gastrinomas can be found almost anywhere, whole-body imaging is required. The initial imaging modality of choice is somatostatin receptor scintigraphy (SRS). Gastrinomas have somatostatin receptors on their cell surface and [^{111}In-DTPA-DPhe^{1}]octreotide, a long-acting somatostatin analogue, can bind to these receptors and localize the tumor. In a study involving 80 consecutive patients with ZES, Gibril and colleagues compared the sensitivity of SRS

performed using [^{111}In-DTPA-DPhe^{1}]octreotide with single-photon emission computed tomography (SPECT) with other conventional imaging methods including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and angiography in detecting primary and metastatic gastrinoma. The primary gastrinoma was identified in 58% of patients using SRS, whereas ultrasound was positive in 9%, angiography in 28%, MRI in 30%, and CT in 31% of patients.[36] When the results of CT were added to those of SRS, an additional 10% of primary lesions (68% total) were able to be identified.[63] De Kerviler and colleagues found that using CT in addition to SRS identified lesions in an additional 12% of patients compared with SRS alone.[64] The size of the primary alters the sensitivity rates of SRS. For example, in 1 study, SRS detected 30% of gastrinomas smaller than 1.1 cm, 64% of those between 1.1 and 2 cm, and 96% of those larger than 2 cm. In summary, because SRS is the single most sensitive study, it should be the initial imaging modality employed for the identification of a primary gastrinoma. CT scanning should be employed in patients in whom SRS fails to localize a primary tumor as the combination of the 2 modalities will identify approximately 70% of primary tumors. Other authors advocate routinely obtaining additional studies such as CT or MRI even if SRS identifies a primary tumor. They note that SRS does not provide information on tumor size or on the exact location of the tumor. For instance, SRS may not be able to distinguish between the presence of the tumor in adjacent structures such as the duodenum versus the pancreas. CT and/or MRI may provide this additional information and, as a result, may influence the surgical approach.[51,65]

In the study by Gibril and colleagues, 24 patients had histologically proven metastatic liver disease and the sensitivities for the detection of any metastatic liver lesion was 42% for CT, 46% for ultrasound, 62% for angiography, 71% for MRI and 92% for SRS.[63] Due to continuing advances in technology, investigators continue to study the role of MRI and CT scanning. A recent study suggests that MRI and CT may be superior to SRS in the identification of hepatic metastases in a series of patients with gastroenteropancreatic endocrine tumors that included gastrinomas. Hepatic metastases were present in 40 of the 64 patients studied as confirmed after liver biopsy or surgery. SRS, CT, and MRI detected a total number of 204, 325, and 394 metastases in these patients, respectively.[66] The authors of this study emphasize the importance of standardizing conventional imaging. Hepatic metastases receive their blood supply preferentially from the hepatic artery. With MRI or CT, therefore, early arterial phase imaging is critical for the detection of these

highly vascular lesions.[66-68] There are several limitations to this study including the fact that, although neuroendocrine-derived liver metastases were pathologically proven in each patient, all lesions identified in this study did not undergo pathological analysis because most of the patients had advanced metastatic disease with numerous lesions and they did not undergo hepatic resection. In addition, almost 20% of the patients were treated during the imaging protocol with a somatostatin analogue that may have affected the results of SRS.[66]

Our current practice for tumor localization in patients diagnosed with gastrinoma is to begin with SRS in an attempt to localize the primary tumor. We also obtain a triple phase CT or MRI to further define the size and location of the primary tumor as well as to look for the presence and extent of hepatic metastases. It is important to remember that even using SRS and complementary conventional studies, the location of the primary gastrinoma will not be detected in approximately 30% of patients.[63] This should not deter one from performing a thorough surgical exploration in patients diagnosed with a sporadic gastrinoma since the majority of lesions, even those not imaged preoperatively, will be identified at the time of exploration. In a series reporting on 35 consecutive patients undergoing surgery for cure, Alexander and colleagues at the NIH detected a gastrinoma in all patients despite the fact that they had failed to identify one third of the lesions preoperatively.[44]

One area of particular weakness for SRS is in the detection of small duodenal gastrinomas. [44,45,51,52,65,69] Because gastrinomas are found 2 to 5 times more often in the duodenum than in the pancreas, this lack of sensitivity in localizing small duodenal gastrinomas is a significant limitation. It was hoped that endoscopic ultrasound (EUS) would be valuable for localizing tumors in the duodenal wall where they are usually smaller than 1 cm. Interestingly, the sensitivity of EUS for the detection of duodenal gastrinomas is less than 50%.[45,70-73] In 1 study evaluating EUS, 57% of the duodenal gastrinomas localized by EUS were seen only on endoscopy, not by US.[45] In contrast, the sensitivity of EUS has been found to be approximately 85% for the detection of pancreatic gastrinomas.[71-74] The routine use of preoperative EUS in an attempt to localize the primary tumor is not universal. Some authors have suggested that EUS may be more helpful in patients with ZES associated with MEN1, where the majority of patients have duodenal gastrinomas but in addition, they often have pancreatic microadenomas or larger tumors. Although EUS will frequently miss the small duodenal gastrinomas similar to the situation with sporadic ZES, it will help define the exact location of additional pancreatic neuroendocrine tumors as well as lymph node

metastases that frequently occur.[20,75,76] Some authors have therefore advocated routinely performing EUS preoperatively in patients with ZES in association with MEN1.[77,78]

Another study that may be helpful in the localization of a primary gastrinoma is hepatic venous sampling of gastrin after the selective intra-arterial injection of secretin. This is a functional study and the advantage of this test is that a positive response does not depend on tumor size. In a series of 92 patients with sporadic gastrinomas treated at the NIH, selective hepatic venous sampling of gastrin levels was positive in 86% of patients.[20] There is currently no consensus on what constitutes the best schema for preoperative localization of gastrinomas and imaging choices should be tailored based on institutional expertise.[79]

Treatment. Before effective medical therapy, more than 90% of patients with sporadic gastrinoma had peptic ulceration and the definitive therapy was a total gastrectomy.[26] In the era of effective antisecretory therapy with H_2-receptor antagonists and PPIs, the rate of total gastrectomy has decreased 5- to 10-fold.[34] Since gastric resection is now rarely required in these patients, surgical treatment is directed at resection of the primary tumor to reduce the risk of subsequent metastatic disease with a goal to improve disease-free and overall survival. Appropriate surgery will result in long-term cure in approximately one third of patients.[20,80-82] Surgical exploration for possible curative resection is therefore recommended for all patients with sporadic gastrinoma without liver or distant metastatic disease and without other illnesses that would limit life expectancy or significantly increase surgical risk.[20]

Up to 30% of patients with sporadic gastrinomas will not have a primary tumor localized before surgical exploration. It is therefore critical that the exploration be performed in a systematic fashion. Either a midline or bilateral subcostal incision may be used. The entire abdominal cavity should be inspected for evidence of metastatic disease. Particular attention is paid to examination of the liver, which is the most common site of metastases. Intraoperative ultrasound is a useful adjunct to staging of the liver and can demonstrate nonpalpable lesions. A wedge resection may be performed for isolated liver metastases either for cure or to control symptoms caused by hormone secretion.[83] The abdominal cavity is also examined for potential ectopic tumors in the liver, stomach, jejunum, ovaries, kidney, and mesentery, which account for approximately 10% to 20% of gastrinomas.[79] Any suspicious lymph node or mass should be evaluated with frozen section examination. An extensive Kocher maneuver is performed to the level of the superior mesenteric vein to allow bimanual palpation and imaging of the pancreatic head and uncinate

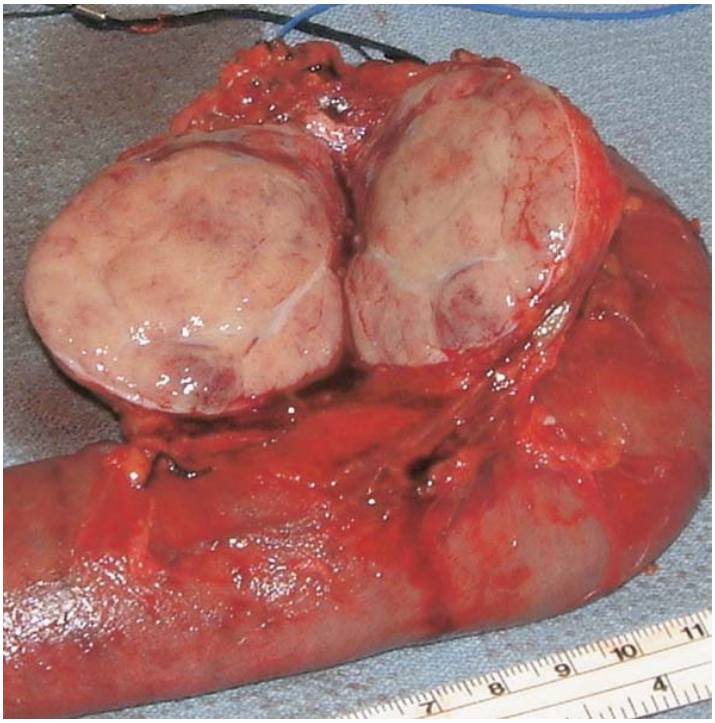

FIG 2. This large gastrinoma in the head of the pancreas required a pancreaticoduodenectomy for removal. (Color version of figure is available online.)

process with intraoperative ultrasound (IOUS). This extended Kocher maneuver is also important for enabling thorough duodenal palpation. The anterior surface of the pancreatic body and tail are exposed by dividing the gastrocolic ligament and entering the lesser sac. Mobilization of the body and the tail of the pancreas is accomplished by incising the peritoneum along the inferior edge of the pancreas from the superior mesenteric vein to the spleen. Mobilization of the splenic flexure allows better inspection, palpation, and IOUS scanning of the pancreatic tail. IOUS is performed with a 10 MHz real-time transducer to identify pancreatic lesions.[84]The combination of bimanual palpation and IOUS will allow detection of virtually all intrapancreatic lesions. Small tumors in the pancreatic head should generally be enucleated and any adjacent lymph nodes are removed, but larger tumors may require pancreaticoduodenectomy (Fig 2). If a tumor is suspected in the distal pancreas, it is resected with a spleen-preserving distal pancreatectomy.[85]

Detection of duodenal lesions is often more difficult. We begin with palpation and IOUS. In addition to palpation and IOUS, another tool that will help to increase the detection rate is intraoperative endoscopy (IOE) with duodenal transillumination. The most important advance in the surgical management of patients with gastrinoma in the last 15 years is

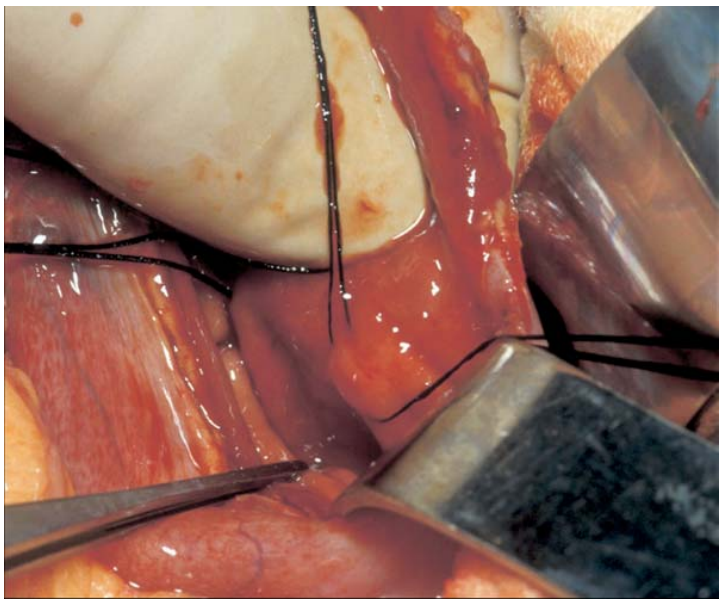

FIG 3. This gastrinoma in the wall of the duodenum was detected by palpation of the duodenal wall after duodenotomy. (Color version of figure is available online.)

the performance of routine duodenotomy.[50,85,86] A 3-cm longitudinal duodenotomy is centered on the anterolateral surface of the descending portion of the duodenum. Careful palpation of the bowel wall along with its eversion can help to identify duodenal gastrinomas, the majority of which are submucosal and are difficult to palpate from outside the bowel lumen (Fig 3). Because duodenal gastrinomas commonly involve the other layers of the bowel wall, treatment consists of a full thickness excision with a small margin of the normal duodenal wall. In a series of 35 patients, Sugg and colleagues were able to identify and excise a gastrinoma in 33 patients.[50] In 27 patients (77%), the tumor was located in the duodenum and the average size was 0.8 cm. A combination of standard palpation after a Kocher maneuver, IOUS, and IOE identified 64% of the lesions. Duodenotomy identified 100% of the tumors. Other recent studies confirm that duodenotomy will detect 25% to 30% of the duodenal tumors that cannot be located by any other modality.[43,85,87,88] A detailed inspection for peripancreatic, periduodenal, or porto-hepatic lymph nodes should be performed. Even if they appear normal, lymph nodes in the region of the head of the pancreas and duodenum should be removed because they may contain microscopic gastrinoma.[49] Routine surgical exploration as described above can be performed safely but results in a long-term cure in only approximately one third of patients. In a series of 123 patients with sporadic gastrinoma undergoing operation at the NIH, Norton and colleagues reported a cure rate of 60% in the

immediate postoperative period. Five- and 10-year cure rates were 40% and 34%, respectively.[20]

There are an increasing number of reports in the surgical literature describing laparosopic resection of pancreatic endocrine tumors, notably insulinomas.[89-94] There is less experience with laparoscopic resection of gastrinomas. There may be a limited role for this operation for several reasons. First, gastrinomas are 2 to 5 times more common in the duodenum than the pancreas and in the duodenum; they are frequently less than 1 cm in size. It has not been established that using laparoscopy, one can reliably find and resect small duodenal gastrinomas. Second, more than 80% of gastrinomas are located in the pancreatic head and laparoscopic resection of lesions in this area is difficult. Finally, laparoscopic resection of an insulinoma has generally been successful when the tumor was found on preoperative imaging and less successful if not identified preoperatively.[95] Up to 30% of gastrinomas are not localized preoperatively so this will likely decrease the success rate using laparoscopy.[96]

Postoperative Management. Before discharging the patient to home after surgical resection of a gastrinoma, it is recommended that at least 2 fasting serum gastrin levels be determined and a secretin stimulation test be performed.[85] One study demonstrated that an immediate postoperative evaluation before discharge that suggests cure (ie, a normal serum fasting gastrin level and a negative secretin stimulation test) was significantly correlated with a 5-year cure.[97] Patients should be maintained on their preoperative antisecretory medications despite a possible cure and should be reevaluated 3 to 6 months after resection. At this time, fasting gastrin levels and a secretin test are repeated. Both tests should be performed because neither one alone detects all recurrences. These biochemical tests should be repeated yearly.[98] It is not necessary to perform routine follow-up imaging studies such as US, CT, or MRI since they are less sensitive than biochemical studies in detecting recurrent disease.[36] It should also be recognized that even in patients cured after resection, some degree of gastric acid hypersecretion may continue and a low dose of an H_2-blocker or PPI may continue to be required.[99] In 1 study, 40% of patients required antiscretory therapy following successful curative gastrinoma resection. There were no laboratory or clinical characteristics that were able to predict the need for continued antisecretory therapy in these patients. The authors recommended routinely evaluating symptoms as well as follow-up esophagogastroduodenostomy when attempting to withdraw drug treatment.[100]

Metastatic Disease. An estimated 60% to 85% of sporadic gastrinomas are malignant.[101] As is the case for other neuroendocrine tumors, the diagnosis of malignancy is generally not made by histology alone but is dependent on the identification of extrapancreatic invasion, or spread to regional lymph nodes or distant sites.[102] Among those patients with malignant gastrinomas, approximately 40% will have metastatic disease at the time of diagnosis, most commonly in the adjacent lymph nodes (30%) and liver (7%).[20] The presence of hepatic metastases is the most important predictor of survival in patients with ZES.[51,55,103,104] Whereas death secondary to complications from ulcer disease was previously common, modern management of gastrinoma using antisecretory agents has made this exceedingly rare. Now tumor progression and metastases are the primary causes of death in 95% to 100% of patients with gastrinomas.[51,105]

Yu and colleagues[55] showed that not only the presence but the extent of liver metastases was an important predictor of outcome. They investigated survival data from 212 patients with ZES. Patients without liver metastases had a 95% 20-year survival, whereas patients with diffuse metastases had a 10-year survival of only 15%. Patients who had metastases confined to a single lobe of the liver or fewer than 5 discrete metastases in both lobes of the liver also had a decreased survival (60% at 15 years); however, it was significantly better than patients with diffuse metastases.[55] Therefore, surgical resection of hepatic metastases has been recommended for a select group of patients. Patients with metastatic disease limited to 1 lobe or less than 5 lesions in both lobes that are resectable should be considered for surgery. Unfortunately, only 5% to 15% of patients have metastatic disease that meets these criteria.[55,75,106-109] In various studies, surgical resection in patients with metastatic neuroendocrine tumors has been performed with acceptable morbidity and low mortality and several authors have reported 5-year survival rates of 71% to 85%.[108-113] Surgery may also play a role in palliation. Palliative resection for uncontrolled hormonal symptoms or pain has been advocated if more than 90% of the tumor burden can be excised safely.[65,112,114,115]

Less than 15% of patients with metastatic disease meet criteria for attempted surgical cure. The majority of patients are therefore managed medically. The initial management of metastatic gastrinoma is expectant observation. Patients receive an antisecretory agent. H_2-blockers can initially control acid secretion in most patients, but over time, most require increasing dosages. Up to 65% of patients on H_2-blockers will ultimately fail.[36] Proton pump inhibitors such as omeprazole are associated with a much lower failure rate (0% to 7.5%) so they are now

considered first line therapy.[36,116] Omeprazole can be started at 60 mg/day and the dose titrated upward. Once symptoms are controlled, it is frequently possible to reduce the dose while retaining its clinical effectiveness.[117] Patients whose symptoms are controlled by antisecretory therapy should be followed with serial CT scans every 3 to 6 months to determine the rate of tumor growth and clinical progression.[83] Additional treatment should be considered in patients who develop abdominal pain, uncontrollable hormone-related symptoms, or rapid, substantial progression of disease on serial CT scans.[83] Additional management options include treatment with a somatostatin analogue, radiofrequency ablation of liver metastases, hepatic arterial embolization, and chemotherapy.

Insulinoma

Insulinomas are, in most series, the most common neuroendocrine tumor of the pancreas. The incidence is approximately 4 cases per million person-years. The median age at diagnosis is 47 years, with a range of 8 to 82 years. There is a slight female predominance (59% of the cases occur in women).[118] The majority of these tumors are solitary, benign, and readily curable with surgical removal. Up to 16% are malignant.

Clinical Presentation. A classic report[119] by Whipple and Franz in 1935 details the history of discovery leading to the appreciation of the disease state associated with hyperinsulinism and insulin-producing islet cell tumors. His description of the symptoms associated with insulinoma is now referred to as Whipple's triad. First, the patient exhibits signs and symptoms of hypoglycemia during fasting. Second, at the time of symptoms, serum glucose is less than 45 mg/dL. Last, the symptoms are relieved by oral or intravenous administration of glucose.

The symptoms and signs commonly associated with hypoglycemia include neuroglycopenic symptoms such as confusion, blurred vision, weakness, or headache and autonomic symptoms including anxiety, sweating, hunger, and palpitations. These patients are often diagnosed with psychiatric or neurologic disorders before the presence of an insulinoma is suspected. In 1 series, patients with insulinomas had symptoms for approximately 3 years before diagnosis.[120] The essential diagnostic test for a suspected insulinoma is a supervised 72-hour fast, during which patients are observed for signs and symptoms of hypoglycemia. Every 6 hours, simultaneous blood draws for blood glucose, insulin, and C-peptide levels should be drawn. If the blood glucose drops below 60 mg/dL, blood draws should be collected more frequently and the test should be concluded if the patient develops symptoms and a blood glucose level below 40 mg/dL. Approximately 70% of patients with

TABLE 2. Causes of hypoglycemia

Endogenous hyperinsulinism due to an insulinoma or nesidioblastosis
Drugs
Alcohol
Sulfonylureas
Insulin
Quinine
Salicylates
Haloperidol
Adrenal insufficiency
Pituitary failure
Hypothyroidism
Hepatic failure
Sepsis
Nonislet cell tumors (most often sarcoma and hepatocellular carcinoma)
Starvation
Postprandial (reactive)
Prolonged exercise

insulinomas will develop hypoglycemic symptoms within 24 hours and up to 98% will do so within 72 hours. An inappropriately high insulin level in the face of hypoglycemia (an insulin-to-glucose ratio greater than 0.3) secures the diagnosis of an insulinoma. Levels of C-peptide and proinsulin should also be elevated in these patients. If they are not, one should look for insulin antibodies and their detection should alert the clinician to the use of exogenous insulin. Patients should also undergo a sulfonylurea screen to exclude the surreptitious use of oral hypoglycemic agents (Table 2).

In equivocal cases, stimulatory tests with secretagogues such as tolbutamide, leucine, glucagon, or calcium have been suggested. These tests have proven to be neither sensitive nor specific.[121,122] The C-peptide suppression test may be more reliable. This test is predicated on the observation that insulin and C-peptide secretion by an insulinoma is autonomous and not suppressed by low serum glucose levels. Plasma C-peptide levels are measured at 15-minute intervals after the injection of 0.1 mU/kg body weight bovine or porcine insulin. A fall in C-peptide levels suggests normal suppression of secretion thus excluding an insulinoma, whereas persistently inappropriately elevated C-peptide levels are indicative of an insulinoma.[123]

Tumor Imaging. Imaging studies should follow a biochemical diagnosis, and are not a substitute for it. Before proceeding with an operation for insulinoma, one should exclude metastatic disease to the liver by either CT or MRI. Some endocrine surgeons believe that beyond excluding metastases, no preoperative imaging is required and that surgeons should

employ careful bimanual palpation of the pancreas with intraoperative high-resolution ultrasonography. This approach should allow identification of at least 90% of insulinomas.[124] Virtually all insulinomas can be found in the pancreas. Those who argue for more extensive imaging before operation cite the financial and emotional costs of a failed exploration.

For those who desire preoperative localization of insulinomas, CT has the advantages of being widely available, relatively inexpensive and noninvasive. Unfortunately, the sensitivity for identifying an insulinoma is variable from as low as 11% to 17%[125,126] to as high as 73%.[127] Imaging technology continues to improve with faster spiral CT providing dynamic imaging and thin slices, so sensitivity may improve. In a recent series from the Mayo Clinic, 19 of 30 (63%) of insulinomas were identified by using multiphasic CT including arterial, pancreatic, and portal venous phases.[128] Most tumors were hyperenhancing and usually seen best on early phase images. Magnetic resonance imaging may be better than CT. Neuroendocrine tumors generally enhance with T2-weighting or with gadolinium contrast. Theoni and colleagues reported identification of 85% of 20 functional small islet cell tumors, including insulinomas using MRI with a 1.5-T magnet.[129] Insulinomas were best seen with T2-weighted fast spin echo or spoiled gradient-echo; however, in some cases gadolinium-enhancement improved identification of the tumor. In another series of 26 patients with insulinomas, MRI with a 0.5-T magnet was 92% sensitive.[130] The optimum and most cost-effective preoperative localization algorithm for a sporadic insulinoma is not established.

The results of EUS are largely dependent on the skill and experience of the operator (Fig 4). The sensitivity is generally reported to be between 70% and 95%; however, the sensitivity is likely to be less for tumors in the region of the pancreatic tail.[131] The addition of EUS in the evaluation of patients in whom CT or MRI has not identified the primary tumor is cost-effective if identification of the insulinoma allows one to forgo more expensive tests such as venous sampling or angiography.[132] This group of investigators from the University of Michigan argues that for patients with a sporadic insulinoma, EUS should be the initial diagnostic test. A French group reported using a combination of thin-cut dual-phase helical CT and EUS to correctly identify insulinomas in all 32 patients seen from 1987 to 2000.[133] This regimen seems to be a cost-effective and efficient preoperative imaging protocol.

SRS with ^{111}In-pentetreotide has a sensitivity of 60%.[134] SRS for the localization of insulinomas is not usually favored due to a relatively low

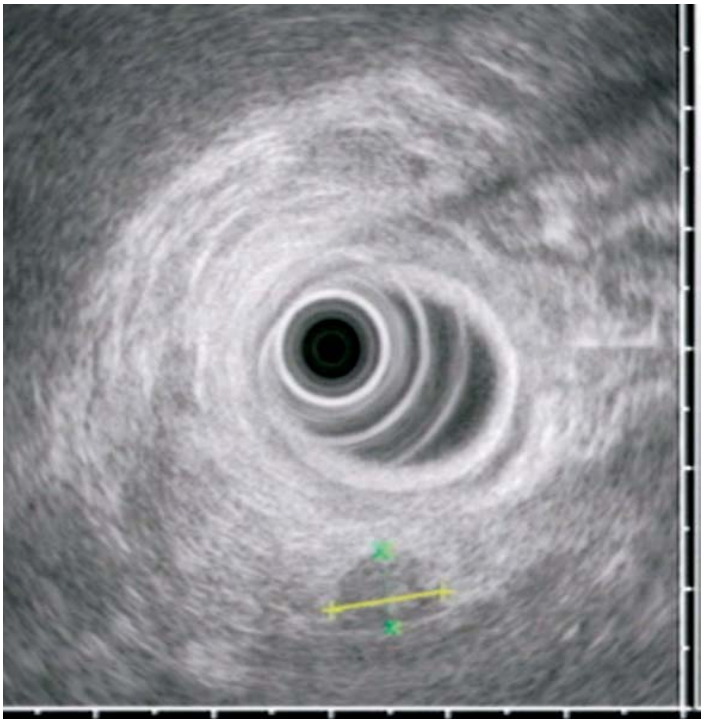

FIG 4. Endoscopic ultrasound image of a small islet cell tumor (marker lines) in the head of the pancreas. (Color version of figure is available online.)

sensitivity and the availability of other modalities.[135,136] The sensitivity of SRS is improved when tomographic images (SPECT) are obtained in addition to planar images, so SPECT should be performed routinely when SRS is employed.[137]

The sensitivity of more invasive imaging techniques such as angiography (36% to 55%) and transhepatic portal venous sampling (55% to 100%) are not appreciably better than the less invasive techniques discussed.[138,139] In 1987, to identify gastrinomas, Doppman and colleagues adapted the Imamura test[140] to locate an insulinoma in 4 patients.[141] Selective injection of calcium as a secretogogue into the arteries supplying the duodenum and pancreas was followed by sampling of blood from the hepatic veins. Rises in insulin and C-peptide levels can be detected 30 to 60 seconds after calcium infusion into the artery supplying the region of the insulinoma.[142] The group from the National Institutes of Health later reported their experience with selective arterial calcium stimulation in 31 patients with insulinomas and reported a sensitivity rate of 94%.[143]

Treatment. The goal of treatment is to remove the tumor surgically. Before proceeding to an operation, however, one should establish a secure biochemical diagnosis of an insulinoma. Accordingly then if one follows

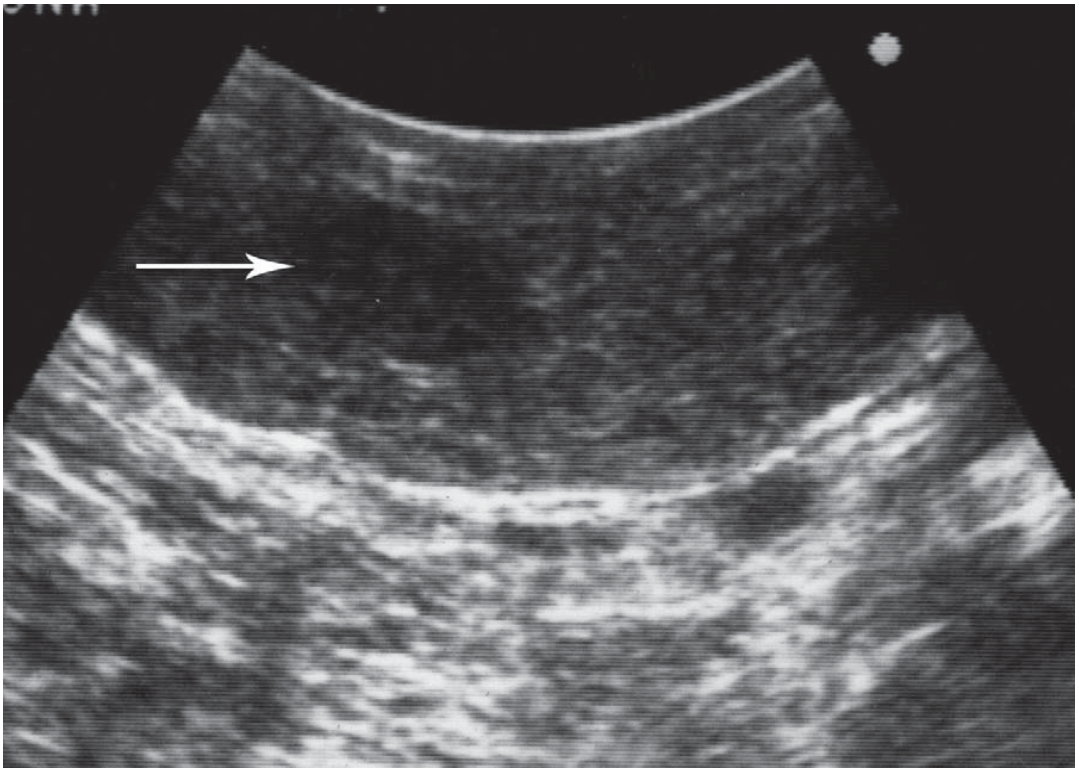

FIG 5. Intraoperative ultrasonography with a high resolution probe shows a small 1 cm insulinoma (arrow) not identified with preoperative MRI or CT. (Color version of figure is available online.)

this principle, inappropriate operations for iatrogenic, factitious, or drug-induced causes of hypoglycemia should be a rare occurrence.[144] Intraoperative ultrasound with a high frequency (10-12 MHz) is an important adjunct to the exploration (Fig 5). If the surgeon is not very familiar with interpretation of ultrasound findings, he should have a radiologist available to come to the operating room. If one chooses not to do preoperative localizing tests, one should be very skilled with intraoperative ultrasonography.[145] One should also monitor glucose levels during surgery and, ideally, also have available the new rapid assay for insulin[146] (Fig 6). A rise in serum glucose and decrease in insulin levels after removal of a pancreatic tumor is indicative of a successful operation.

A midline incision or a bilateral subcostal incision may be used to enter the abdomen. A careful and thorough exploration of the liver as well as portal and peripancreatic lymph nodes is conducted to assess for possible metastases. Even if preoperative studies have identified the location of the insulinoma, the entire pancreas should still be explored because 13% to 24% of patients have multiple insulinomas.[147,148] For tumors of the head of the pancreas, an extensive Kocher maneuver is performed by incising the lateral peritoneal attachments of the duodenum. In this manner, one

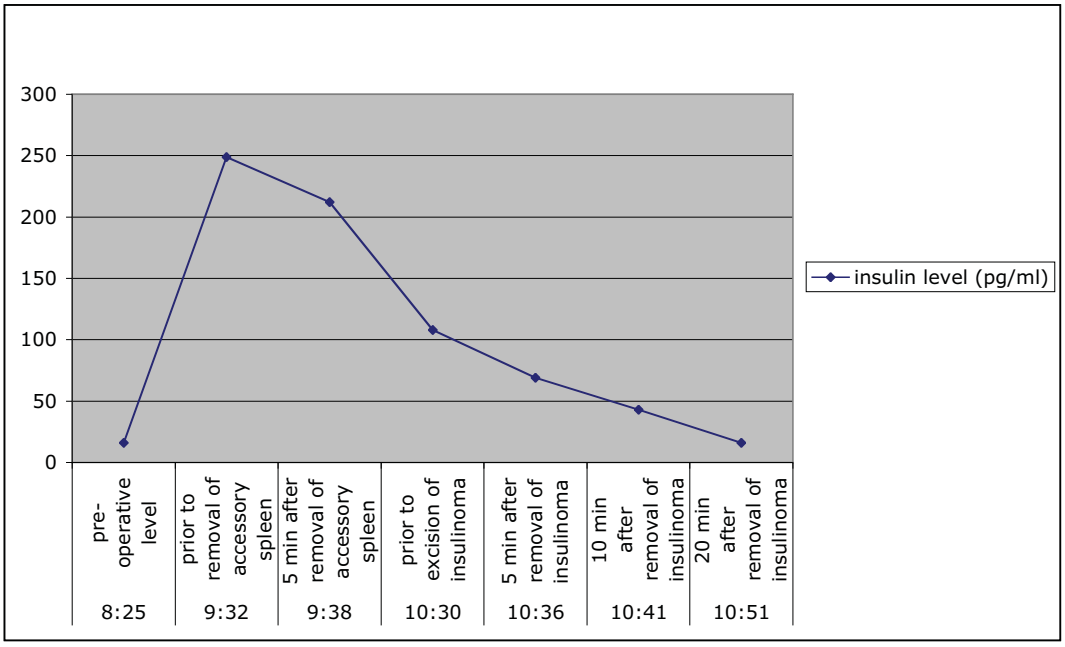

FIG 6. Graph depicts the results of the rapid insulin assay (Future Diagnostics) done during the course of an operation to remove an insulinoma, noting time and stage of the operation. One can see a rapid drop in the insulin level within minutes after removal of the insulinoma. (Color version of figure is available online.)

can carefully feel the head of the pancreas head and conduct a thorough ultrasound evaluation of the head and uncinate process. One must then decide whether the tumor may be safely enucleated or whether a pancreaticoduodenectomy is needed. For tumors of the body or tail of the pancreas, the lesser sac is entered through the gastrocolic omentum. The stomach is retracted in an upward direction and the anterior surface of the pancreas is identified. The peritoneum along the superior and inferior aspects of the body and tail of the pancreas is incised. The pancreas can then be palpated between the thumb and forefinger or between the fingers of 2 hands. Often, an insulinoma can be seen on the anterior surface of the pancreas. They typically appear as a reddish tan to brown nodule. A tumor that is not visible may be felt as a firm area within the pancreatic parenchyma. Intraoperative ultrasound is a useful adjunct to establish the relationship of the insulinoma to the pancreatic duct and splenic vessels. In some cases, resection may be safer in that the risk of fistula may be lower than for enucleation. Since most insulinomas are benign, a splenic-preserving distal pancreatectomy is generally preferred to an en bloc resection of the tail of the pancreas and spleen (Fig 7).

For enucleation, one must have good exposure and control of the pancreas. The lesion is approached with a fine hemostat, electocautery,

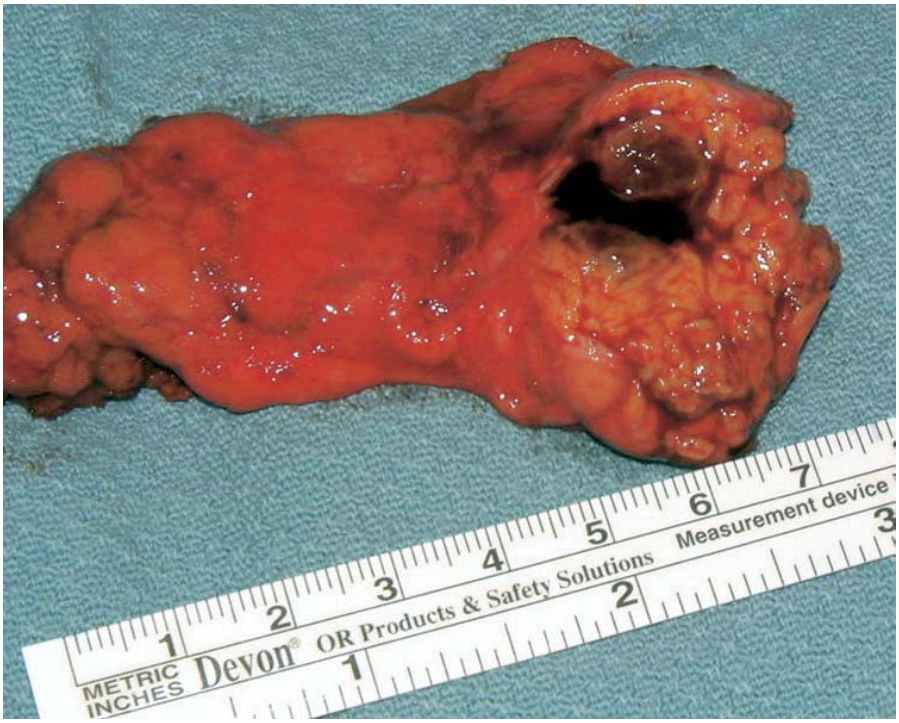

FIG 7. Typical insulinoma in the tail of the pancreas. A hand-assisted laparoscopic splenic preserving distal pancreatectomy was performed to remove the tumor. (Color version of figure is available online.)

and small hemostatic clips. The site of the resected tumor should be carefully inspected for evidence of the leakage of clear watery fluid indicative of pancreatic juice. Administration of 1 mg of secretin stimulates increased production of pancreatic juice and may facilitate identification of an injury to the pancreatic duct. If identified, pancreatic resection should be considered. If no leak is present the defect in the resection bed may be closed gently or plugged with omentum. The perioperative use of somatostatin analogues such as octreotide or vapreotide does not appear to reduce the rate of pancreatic fistula formation after pancreatic resection,[149] so it does not seem likely that it would be of benefit in preventing a pancreatic leak after enucleation. Similarly, there is no proof that tissue sealants reduce the risk of pancreatic fistula rates, but some surgeons still recommend their use. The senior author places a closed drain near the tumor resection site.

Because they are generally small and benign, insulinomas are perhaps the pancreatic tumors best suited for resection by a laparoscopic approach. In 1996, Gagner and colleagues reported a series of 12 patients with islet cell tumors of the pancreas, most of them insulinomas, who underwent attempts at either laparoscopic distal pancreatectomy or enucleation of their tumors.[150] One could question the success of this

early experience since 4 patients were converted to open procedures, and in 2 patients, the insulinoma was not found. The threshold was crossed, however, and several reports have followed demonstrating that laparoscopic surgery for insulinomas is possible and offers the advantages of minimally invasive surgery to this group of patients.[151,152] The list of procedures reported now includes distal pancreatectomy with preservation of the spleen.[153] Limitations remain and include a relatively high fistula rate and the technical demands of the procedure are associated with prolonged operative times. A hand-assisted approach may be ideal in some cases because one may need to palpate the pancreas for a small insulinoma and the patient will derive the benefits of a small incision. Presently, the laparoscopic approach is not indicated for insulinomas in the setting of MEN1 or for malignant or large tumors. The report by Fernandez-Cruz and colleagues contains an excellent description of the conduct of the operation and the reader is referred to it for details of the procedure.[151]

In the event pancreatic exploration is unsuccessful in locating an insulinoma, a distal pancreatectomy should be performed only if one has established that the location of the insulinoma is in the pancreatic tail, by means of an invasive test such as selective arterial secretagogue injection (SASI). Despite recommendations by some authors in the past,[154] a "blind" distal pancreatectomy should not be performed. It is just as likely, or perhaps more so, that the missed insulinoma is in the pancreatic head or uncinate as it is in the tail. It is better to close the patient's abdomen, control the symptoms with medications, and embark on a search for the missing insulinoma or establish whether the patient has a rare case of adult nesidioblastosis.

Postoperative Management. Glucose levels should be monitored closely during the operation. Intravenous infusion with dextrose solution is used to maintain the serum glucose level in an acceptable range. One typically sees a rise in the serum glucose level within 20 minutes after successful removal of an insulinoma; however, this response may be delayed.[155] One should be cautious, however, because false positives and negatives do occur.[156] Generally, the serum glucose levels will rise to the 200 to 300 mg/dL range for several days to 3 weeks after successful surgery and then gradually blood sugar levels will return to normal.[157] Recently, Carniero and colleagues reported on the use of a rapid chemiluminescent assay for insulin.[146] Assay results were available within 8 minutes, making this a useful intraoperative adjunct. In this report, 8 consecutive patients underwent pancreatic resection for insulinomas. In the perioperative period, the patients were infused with 10%

dextrose at a rate sufficient to maintain their blood sugars levels near 150 mg/dL. Blood levels of insulin were determined at the start of operation, during dissection of the pancreatic tumors, and after removal of the insulinoma. These authors recommend that the criteria for a successful curative resection be as follows: (1) the return of insulin levels to normal (10-86 pmol/L) 15 minutes after tumor removal, and (2) an insulin-to-glucose ratio of less than 0.4. These authors do warn that diazoxide may interfere with performance of this assay in these patients. An advantage of this particular system (Future Diagnostics, Wijchen, Netherlands) is that the insulin assay can be performed with the same equipment that is used for intraoperative parathyroid hormone assay. Otherwise, the purchase of such equipment for use in a rare number of cases would be difficult to justify from a financial perspective alone. These authors also suggest, as they did in 1 case, that one perform a fine needle aspirate of a suspicious nodule and eject the contents into 1 mL of saline. One should see a high insulin level in the saline if the tumor biopsied is an insulinoma. The optimum criteria predictive of a cure remain to be established. Proye and colleagues suggested one should see normal peripheral and portal vein blood insulin levels 20 minutes after resection.[158]

Adult Nesidioblastosis. Organic hyperinsulinism due to hypertrophy of the β-islet cells is a well known phenomenon in neonates but a rare event in adults.[159,160] The Mayo Clinic group has reported on a series of 10 patients with what they term as noninsulinoma pancreatogenous hypoglycemia.[161] These patients all had biochemical evidence suggestive of an insulinoma, yet no tumor was found. Preoperative selective arterial calcium stimulation guided surgeons to a distal pancreatectomy. Pathologic examination of the operative specimens demonstrated islet cell hypertrophy or nesidioblastosis. Eight of the 10 patients had improvement in their hypoglycemia. It seems logical that intraoperative insulin level and glucose monitoring would be particularly useful in this patient population to guide the extent of pancreatic resection.

Malignant Insulinomas. Approximately 10% of insulinomas are malignant. The behavior of malignant insulinomas tends to be fairly indolent although progressive. One 60-year study from the Mayo Clinic found a 10-year survival rate of 29%.[162] A malignant insulinoma should be suspected if the primary tumor is larger than 3 cm. In all cases, one should carefully evaluate the liver and peripancreatic lymph nodes for evidence of metastatic disease. Suspicious lymph nodes should be sampled for histopathology. For lesions in the body and tail, an en bloc distal pancreatectomy and splenectomy with nodal dissection should be per-

formed. For malignant insulinomas of the pancreatic head or uncinate, a Whipple procedure is recommended. Even if a cure is not possible, an aggressive surgical approach to debulk tumor and resect liver metastases is warranted to ameliorate hypoglycemic symptoms. Although there are no prospective randomized series, single institution retrospective series suggest complete surgical resection can improve survival. McEntee and colleagues reviewed their experience with 17 patients who underwent complete resection of neuroendocrine metastases to the liver.[163] Of these, 11 (65%) were alive and free of disease at a mean follow-up interval of 19 months.

Carcinoid Tumor

More than 60% of carcinoid tumors reside in the gastrointestinal tract, most commonly in the small intestine, appendix, and colon. Pancreatic carcinoid tumors are unusual and comprise only approximately 0.6% of all carcinoid tumors and only approximately 2% of gastrointestinal carcinoid tumors.[164,165] The first report of a pancreatic carcinoid tumor was by Pataky and colleagues in 1959.[166] The average age of the patients in large series of 156 patients was 48.9 years with a slight female predominance.[167] In this same series, carcinoid symptoms were present in 23% of patients and consisted of abdominal pain (40.4%), diarrhea (30.8%), and flushing (19.9%). Carcinoids were more frequently seen in the head of the pancreas (44.9%) than in the body or tail. The average size of the pancreatic carcinoids in this series was 6.8 cm and metatases were present in two thirds of patients. The 5-year survival rate was relatively low at 28.9%, compared with other carcinoid tumors of the small intestine (82.1%) or appendix (89.7%).

VIPoma

Tumors expressing excess vasoactive intestinal peptide, or VIPomas, rank third in frequency among islet cell tumors, after insulinoma and gastrinoma, producing defined endocrine syndromes. The Verner-Morrison syndrome produced by these tumors is also called pancreatic cholera and the WDHH or WDHA syndrome for watery diarrhea, hypokalemia, and hypochlorhydria or achlorhydria. The median age at presentation is 47 years, with a range of 17 to 72 years, and women are afflicted 3 times more frequently than are men.[168] The typical clinical presentation is with profuse watery diarrhea. Because the diarrhea is secretory, fasting does not alter its severity and crampy abdominal pain is not a common feature. Characteristically, patients may have 10 to 15 bowel movements daily producing up to 10 L of tea-colored liquid stool. This stool is rich in

electrolytes so patients may lose up to 300 mEq of potassium every 24 hours leading to hypokalemia. The mean serum potassium level at presentation is 2.2 mEq/L. Metabolic acidosis is likely due to hypochlorhydria and loss of bicarbonate. Hypercalcemia occurs in approximately one half of patients. Patchy erythema and urticaria of the skin of the face and trunk is present in approximately 20% of patients.[169] Other occasional findings include hypomagnesemia, an abnormal glucose tolerance test, psychosis, or a large atonic gallbladder.

The diagnosis is established by documenting an elevated serum VIP level, above 200 mg/mL, by radioimmunoassay. Other endocrine tumors associated with diarrhea include gastrinomas, carcinoid tumors, and medullary thyroid cancer. Surreptitious use of laxatives may result in diarrhea that mimics the presentation of a VIPoma. Because the serum VIP levels may be elevated in these patients, laxative abuse should be excluded by testing of stool by chromatography or spectrophotometric assays for candidate laxatives. Celiac sprue may be distinguished from the WDHH syndrome by means of a D-xylose absorption test and small bowel biopsy. Furthermore in celiac sprue, the diarrhea resolves with fasting.

Approximately 50% of VIPomas are malignant, of which three fourths have presented with metastases at the time of diagnosis.[170,171] There is no curative treatment for tumors that are not completely resectable. The median survival in this setting is approximately 1 year.[172] For resectable tumors, preoperative preparation has been greatly facilitated by the use of somatostatin analogues such as octreotide. Before this time, corticosteroids and indomethasone were used to alleviate the diarrhea, but currently have no place in treatment protocols. Octreotide controls the diarrhea and allows for rehydration and correction of electrolyte derangements. Operative exploration should include a careful examination for evidence of metastatic spread. Intraoperative ultrasound is an important adjunct not only for examination of the liver, but for examination of the pancreas for a potentially small islet cell tumor that is difficult to feel. In the collected review of 55 patients with VIPomas by Verner and Morrison, 20 had benign islet cell tumors, 22 had malignant islet cell tumors, 12 had islet cell hyperplasia, and 1 had no discernible pancreatic abnormality.[170] Careful bimanual palpation of the entire pancreas requires an extensive Kocher maneuver and incision of the retroperitoneum superior and inferior to the body and tail of the pancreas. Approximately 10% of VIPomas are ectopic.[173] These occur along the ganglia of the autonomic nervous system or adrenal medulla. Other reported ectopic sites of

VIPomas include the retroperitoneum, jejunum, bronchus, and esophagus.[174,175]

Glucagonoma

Glucagonomas are rare tumors that occur once in 20 to 30 million person-years.[176] Glucagonomas arise from the alpha or A islet cells of the pancreas. Glucagon is a 29-amino-acid single chain polypeptide. Its primary function is to promote gluconeogenesis, glycogenolysis, and ketogenesis. Glucagon also stimulates the secretion of insulin and promotes lipolysis in adipose tissues. The release of glucagon is stimulated by consumption of a high-protein meal, hypoglycemia, starvation, and stress. The result of glucagon excess is hyperglycemia. The relatively mild diabetes mellitus usually does not require insulin administration for control of blood sugar levels. Patients with tumors that produce excess glucagon exhibit a characteristic rash known as necrolytic migratory erythema (Fig 8). The rash is pruritic and generally begins on the extremities before spreading to the truck and face. Although necrolytic migratory erythema is a characteristic feature of glucagonoma, it is often not recognized for what it is. It may have been present for 1 to 6 years before the diagnosis is made.[177] The rash is often misdiagnosed as psoriasis, eczema, or zinc deficiency. Other clinical features may include weight loss, hypercalcemia, glossitis, and thromboembolic disease. Approximately 90% of patients have lost more than 5 kg of body weight.[178] Muscle wasting appears to be out of portion to tumor burden and may related to the severe decrease in plasma amino acid concentrations seen in these patients.[179] An increased risk of thromboembolic disease is attributed to increased production of factor X by pancreatic A islet cells.[180] Deep vein thrombosis and pulmonary emboli are not uncommon and can be fatal.

The characteristic necrolytic migratory erythema rash is pathognomonic, and the clinical picture should lead one to the diagnosis. An elevated serum glucagon level above 190 pg/mL confirms the diagnosis. Metastases are present in 60% to 80% of cases at the time of diagnosis. Most glucagonomas are solitary tumors and typically occur in the body or tail of the pancreas. Localization is not often a problem because these tumors are usually 4 to 10 cm in diameter and readily identified by CT.

Because glucagonomas are potentially malignant tumors, they should be treated as such with resection with clear margins rather than by enucleation. The only chance for cure is complete surgical resection. Before operation, preparations should include control of

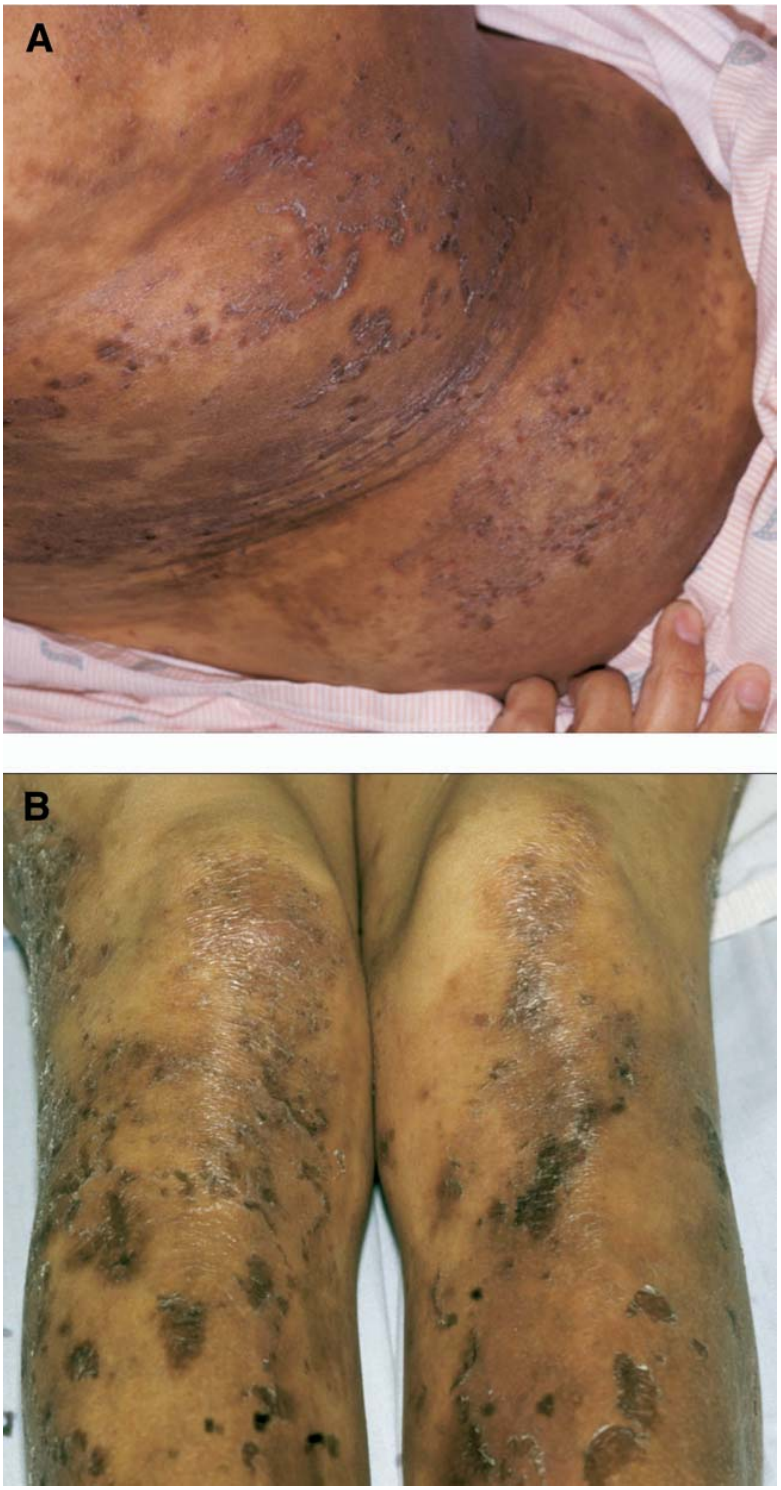

FIG 8. The characteristic rash associated with a glucagonoma, necrolytic migratory erythema, demonstrated in these photographs of the trunk (A) and legs (B) resolves rapidly after removal of the tumor. (Color version of figure is available online.)

blood sugar levels, nutritional assessment, and alimentation as necessary. Perioperative prophylaxis with subcutaneous heparin is indicated. Some have suggested that octreotide, because it decreases the circulating glucagon levels, may allow for improved preoperative nutritional benefit of alimentation, healing of rash, and reduced risk of thromboembolism.[181] Resection of the rash results in resolution of the necrolytic migratory erythema rash within a few weeks. Similarly, lost body weight returns.

Somatostatinoma

Somatostatin is an inhibitory tetradecapeptide produced by the pancreatic islet D cells. It has effects on the release of most all gut peptides and secretory function of the stomach, duodenum, and pancreas. Somatostatin has also been identified in a variety of tissues including cells in the stomach, small intestine, salivary glands, and thyroid. Excessive production of somatostatin by a pancreatic islet cell tumor leads to a clinical syndrome manifested by steatorrhea, diarrhea, mild diabetes mellitus, cholelithiasis, weight loss, anemia, and hypochlorhydria.[182] These symptoms and findings may be explained by the physiologic activity of somatostatin that inhibits the release or actions of almost all gut hormones including insulin, glucagons, gastrin, and cholecystokinin. Islet cell tumors secreting somatostatin are exceedingly rare. In the largest collected series published, 48 patients with somatostatinomas were included.[183] Of these, 27 patients had pancreatic primary tumors and 21 had intestinal tumors. The mean age of the patients at presentation was 51 years, ranging from 26 to 84 years of age. Twenty-seven (56%) were women and only 26% of patients were free of metastases at presentation.[184] In their review, Vinik and colleagues made distinctions between the presentation of patients with pancreatic somatostatinomas compared with those whose tumors originated within their intestines.[183] Patients with pancreatic tumors have higher plasma concentrations of somatostatin-like immunoreactivity and were more likely to be women. Furthermore, diabetes mellitus, gallbladder disease, and steatorrhea occurred in the majority of patients with pancreatic lesions but were relatively infrequent conditions among those with intestinal somatostatinomas. In these patients, diabetes tends to be mild and can be controlled usually with oral hypoglycemic agents. Gallbladder stones do not generally cause symptoms and the steatorrhea is attributed to the inhibition of the secretion of pancreatic digestive enzymes that digest fats.

The first well-documented case reported, in 1977, was that of a middle-aged woman with abdominal pain and steatorrhea.[185] Over the

ensuing 10 years, she developed headaches, tachycardia, and flushing. Ultimately at the time of operation for a cholecystectomy, she was found to have a tumor in the head of her pancreas and liver metastases. This presentation is typical in that the diagnosis may elude physicians and that metastatic disease at diagnosis is present in 85% of cases. In addition to the liver, other common sites of metastases included the regional lymph nodes and bones.

Due to the rarity of this disease, the optimum treatment has not been established. Current recommendations[186] for small (<2 cm) tumors in the wall of the intestines and with no evidence of metastases is for the tumor to be treated by local excision or wedge resection. For large tumors of the duodenum or the pancreatic head, a pancreaticoduodenectomy is generally required. In general, however, a radical resection should not be performed in the presence of distant nodal or liver metastases. Tumors in the body and tail should be resected when possible, even in the presence of metastases, when preoperative symptoms suggest debulking may provide palliation.

ACTH-Mediated Cushing's Syndrome

Cushing's disease with the signs and symptoms of cortisol excess was initially described in 1932. The great majority of cases are due to pituitary adenomas producing excess adrenocorticotropic hormone (ACTH). An ectopic source of ACTH accounts for only approximately 12% of the cases, and usually this is a small cell lung cancer.[187] In 16% of these cases, an islet cell tumor of the pancreas producing ACTH is the source. ACTH-producing pancreatic islet cell tumors are rare and generally behave in an aggressive manner.[188] A review of the literature shows 74 reported cases, of which 62% are women. Liver metastases were present in 69% of cases at presentation. The median survival was less than 2 years and the 5-year survival rate was only 16%.[189] Death usually resulted from infectious complications that may be, at least partially, the result of cortisol-induced suppression of the immune system.[190] It is, therefore, important to control hypercortisolism surgically or medically as part of the management of these patients when they present with an opportunistic infection. Another feature of these tumors is that, interestingly, some have observed that ACTH-producing islet call cancers of the pancreas may also produce gastrin in levels sufficient to cause coexistent Zollinger-Ellison syndrome.[191] For patients with metastases for whom symptoms are difficult to control with medications, bilateral adrenalectomy is an option and may be helpful.

PTH-Related Peptide

One of the rarest functional islet cell cancers is the tumor that makes parathyroid hormone-related peptide (PTH-rP). The notable feature of this tumor is profound hypercalcemia, with a low parathyroid hormone level. Review of the literature shows only approximately 20 cases reported in the English literature.[192,193] PTHrP is chemically similar to the structure of PTH in that it possesses homology to PTH at the amino terminus. It is capable of binding to and activating the PTH receptor in the kidneys and bones so as to cause hypercalcemia.[194] Medical management of the hypercalcemia with hydration, furosemide, somatostatin analogues,[195] and diphosphonates is suboptimal. Because in general these cancers grow slowly, resection with debulking or ablation of liver metastases is warranted when possible to control hypercalcemia. Treatment of liver metastases with hepatic artery chemoembolization may help control calcium levels in patients with unresectable liver tumors.

Nonfunctioning Pancreatic Neuroendocrine Tumors

These tumors usually manifest in the fourth or fifth decade of life. When they occur outside the setting of a predisposing genetic syndrome such as MEN1, nonfunctioning neuroendocrine tumors are typically solitary with approximately 60% occurring in the head of the pancreas. Nonfunctioning tumors are typically larger than functioning tumors at presentation because they do not produce symptoms of hormone excess. Symptoms related to the pancreatic mass may include abdominal or back pain, nausea, fatigue, and weight loss. It is believed that 10% to 15% of these tumors are discovered incidentally by radiologic imaging or during intra-abdominal exploration for other indications. Patients with a suspected pancreatic neuroendocrine tumor without features suggestive of hormone excess should still have serum markers assayed. Serum chromogranin A and neuron-specific enolase (NSE) are the most frequently used. Other investigators have also suggested pancreatic polypeptide (PP) and the β subunit of human chorionic gonadotropic hormone (βHCG) as tumor markers. Appearance of a pancreatic neuroendocrine tumor on CT after intravenous contrast is typically enhancing relative to the surrounding parenchyma, but may be hypodense or even cystic appearing. Endoscopic ultrasound is increasingly used as a diagnostic modality allowing a skilled operator to discern the relationship of a pancreatic tumor to the celiac artery and the superior mesenteric vessels. Endoscopic ultrasound-guided fine needle cytology is now the preferred method for

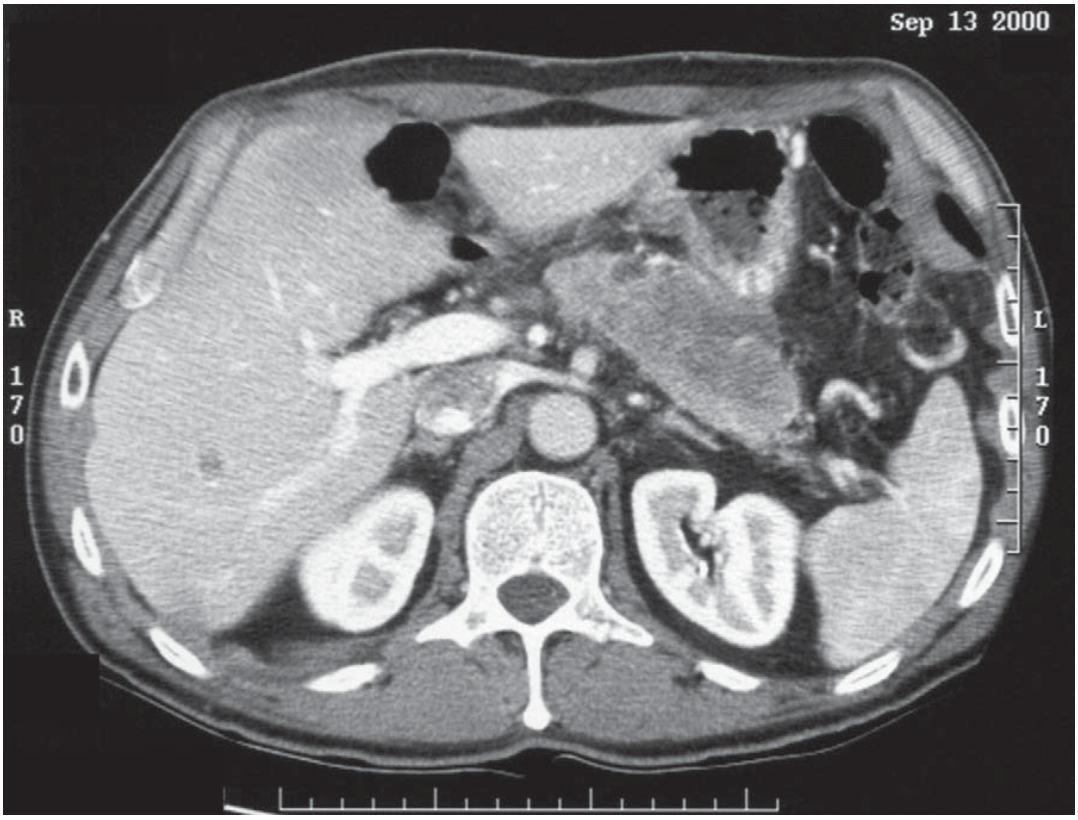

FIG 9. This nonfunctional islet cell cancer was treated by resection of the primary tumor and ablation of the solitary liver metastasis.

obtaining a preoperative tissue diagnosis, if required. Resectability is ascertained in a manner similar to pancreatic adenocarcinoma, but some have advocated resection of a tumor in the tail even in the presence of liver metastases (Fig 9). This approach is justified by citing the relatively indolent clinical course of many patients with stage IV islet cell cancers and is predicated on the efficacy of many liver directed treatments including ablative modalities and intra-arterial chemoembolization. Others, however, state that overall survival is not improved when a primary tumor is resected in the presence of liver metastases.[196] It would seem reasonable to proceed with resection only if the extent of liver metastases is limited.

The clinical outcome of patients with nonfunctioning pancreatic neuroendocrine tumors was reported by investigators at MD Anderson.[197] In this series of 163 patients, the median age was 52 years and the ages ranged from 20 to 88 years. Although the median tumor size was 6 cm, sizes ranged from 1 to 25 cm and tumors occurred with roughly an equal frequency in the head, body, or tail of the pancreas. Abdominal pain was the most common presenting symptom, occurring in 75% of the patients.

Other presenting signs and symptoms included painless abdominal masses, jaundice, weight loss, and severe hemorrhage from the tumor.[198,199] Overall median survival in the MD Anderson series was 3.2 years and the 5-year survival rate was 43%. Median survival was significantly better for those with localized disease (7.1 years) than it was for those with metastases at the time of presentation (2.2 years). The results were notable also in the observation that only 20 (48%) of the 42 patients in this series who were able to undergo resection with curative intent were free of disease at their last follow-up visit. Therefore, although the overall prognosis is better than that associated with adenocarcinoma of the pancreas, relatively few patients are cured of their islet cell cancers.

Genetic Syndromes Associated with Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors are relatively uncommon solid lesions arising in the pancreas and are broadly classified as functional or nonfunctional. These tumors are associated with 4 distinct familial syndromes: multiple endocrine neoplasia type 1 (MEN1), von-Hippel Lindau (vHL), neurofibromatosis (NF-1), and tuberous sclerosis (TSC 1/2). Each of these syndromes has distinctly different genotypes and phenotypes; however, the pancreatic manifestations can have certain similarities.

Pancreatic Islet Cell Tumors Associated with Hereditary Genetic Disorders

Multiple Endocrine Neoplasia Type 1

Multiple endocrine neoplasia type 1 (MEN1) is a relatively uncommon inherited disorder, although it is probably the most common of the inherited disorders resulting in pancreatic neuroendocrine tumors. MEN1 results from a mutation in the tumor suppressor gene MEN1, which was mapped and positionally cloned to the long arm of chromosome 11 (11q13).[200,201] Neoplasms occurring in the pancreas, parathyroid, and pituitary gland characterize the syndrome and when these lesions are examined at a molecular level, loss of heterozygosity is seen at the MEN1 locus. Studies have demonstrated that alterations within the MEN1 gene affect the ability of its product, menin, to interact appropriately with the JunD/activator protein-1, NF-κB, and Smad3 signaling pathways that are important in transcription and regulation of cell growth.[202,203] Multiple endocrine neoplasia type 1 is present in between 1 and 10 per 100,000

individuals.[203] There is increasing penetrance as individuals harboring this mutation increase in age, from a low of 7% at 10 years to a high of 80% to 100% at 50 years.[203] This is true for the penetrance of pancreatic neuroendocrine tumors, which has been reported to be 15% at age 30 years and 68% by age 70 years.

The diagnosis of MEN1 is made through obtaining a careful family history and documentation of other members of the family who have manifestations of MEN1 as well as a determination of the presence of at least 2 principal MEN1 tumors in the individual being evaluated. These 2 tumors can be either a pituitary adenoma, primary hyperparathyroidism, or a neuroendocrine tumor of the pancreas or the duodenum. In patients who have a first degree relative with 2 or more of these tumors the presence of only 1 of these tumors is required to establish the diagnosis.[204] The role for genetic analysis in these patients is undergoing evolution. There are several options for determining the presence of genetic perturbations at the MEN1 locus including sequencing, haplotype testing, and trait testing for tumor emergence.[204-206] The diagnosis of a pancreatic neuroendocrine tumor is made either through the demonstration of the presence of symptoms due to hormonal production (as well as serum evidence of the hormone) or at the time of a screening ultrasound or abdominal CT scan looking for lesions in the pancreas. The 2 most common functional neuroendocrine tumors seen in association with MEN1 are gastrinoma and insulinoma.

Gastrinomas can occur in both the duodenum and the pancreas, with the higher proportion of these lesions occurring in the duodenum.[207] Foregut carcinoids are rarely functional and can be confused with gastrinomas because they occur in similar locations. Zollinger-Ellison syndrome with its elevations in gastric acid production can be found in association with MEN1. This syndrome can be managed effectively with medications, which lower acid production. The life-threatening ulcers as a result of this condition, which previously necessitated extensive gastric resections, are rarely if ever presently seen. Such operations are no longer necessary in the majority of cases due to the improvements in both H_2-blockers and PPIs. However, there is evidence that gastrinoma can result in life-limiting metastatic disease, which may require surgical intervention for the primary to prevent distant spread. Studies have shown that surgery for ZES can alter the natural history of both sporadic and MEN1 gastrinoma.[208,209] Therefore, surgery in selected patients may alter the natural history of these lesions. The diagnostic evaluation of gastrinoma in patients with MEN1 parallels the evaluation of these lesions in sporadic cases. Documentation of fasting serum gastrin levels along with increased

basal acid output and, in some cases identification of a lesion in the duodenum, establishes the diagnosis. The surgical approach to the management of these patients involves preoperative imaging with both contrast-enhanced CT scan as well as somatostatin receptor scan (SRS) to locate potential sites of lymph node or distant metastatic disease. The primary gastrinoma lesion tends to be a small submucosal tumor located in the duodenum and is impossible to detect with noninvasive imaging modalities. These lesions can often be seen by performing upper gastrointestinal endoscopy at the time of surgical exploration where visualization combined with palpation can lead to the identification of these lesions.[20,97] At the time of surgical exploration the duodenum and head of pancreas are mobilized in the usual fashion and a duodenotomy is performed after endoscopic visualization to locate these lesions. A local resection is then performed for the majority of cases. Locally involved lymph nodes visualized by CT or scintigraphy, or found at the time of exploration, are then also resected. For patients with evidence of metastatic spread, most commonly to the liver, resection or ablation of these lesions can be performed.

Insulinomas can also be seen in association with MEN1. The biochemical diagnosis is made in a similar fashion to that made for sporadic cases.[210] Once a biochemical diagnosis of insulinoma is made through the appropriate supervised fast and blood work, imaging studies are then performed to identify the location of the lesion. In contrast to gastrinomas, these lesions are most often found in the pancreas gland. Confounding such localization in patients with MEN1 is the fact that these patients may have multiple lesions in their pancreas, the majority of which are nonfunctional tumors. Therefore, techniques that allow one to differentiate the functional insulinoma from other nonfunctional islet cell tumors in the pancreas may be of value. Some investigators approach the management of patients with neuroendocrine tumors of the pancreas with a standardized surgical approach, which consists of enucleation of all visualized lesions in the head of the pancreas and an extended distal pancreatectomy to remove remaining tumors and tissues at risk. Such an approach will remove functional tumors as well as the majority of nonfunctional tumors in the pancreas, thereby decreasing the risk of metastatic spread.[211] An alternative approach is to attempt to identify those functional lesions and to remove only those nonfunctional lesions that are larger than 3 cm in size.[212] A variety of techniques have been developed in an attempt to functionally locate a neuroendocrine tumor, which produces an active hormone. Preoperatively, a calcium-stimulated arteriogram can be used to determine the region of the pancreas where

such a lesion is present.[213,214] Such a study is based on the fact that an infusion of calcium via an artery supplying a region of pancreas acts as a secretagogue to stimulate the neuroendocrine tumor in that region to secrete its protein product. The presence of such a product can then be sampled in hepatic veins. Such an approach can be very accurate in localizing the region of the pancreas (head, neck, body, or tail) that contains the tumor of interest. Once in the operating room, lesions are identified by inspection, palpation, or ultrasound. If desired, a fine needle aspirate can be performed of the putative tumor with a rapid determination of the aspirate's insulin value intraoperatively to confirm the identity of the insulinoma and guide the resection.

In addition to gastrinoma and insulinoma several other functional neuroendocrine tumors have been associated with MEN1 including glucogonoma and VIPoma syndromes. The approach in these patients is similar in that once the diagnosis is made, surgical resection of these lesions is recommended. The majority of pancreatic neuroendocrine tumors associated with MEN1 are nonfunctional. Therefore, the management of such lesions is predicated on the concern that if left untreated such lesions can eventually metastasize and limit life expectancy. Studies have demonstrated that lesions larger than 3 cm pose a greater risk for metastasis and therefore a selective approach has been developed to manage nonfunctional lesions when they reach a size threshold.[201,212,215] Others approach these nonfunctional lesions more aggressively and employ a standard surgical approach consisting of enucleation of all head lesions and a subtotal distal pancreatectomy in all patients diagnosed with pancreatic lesions regardless of the size of the lesions.[211] Both approaches have potential benefits with respect to prolonging disease-free interval and in experienced hands such operations can be accomplished with relatively low morbidity and mortality. For nonfunctioning tumors, tumor markers such as pancreatic polypeptide may be useful for determining recurrence or for documenting distant disease. In such patients somatostatin scintigraphy (octreotide scanning) can be useful for determining the extent of disease.

Von-Hippel Lindau (vHL) Syndrome

Von-Hippel Lindau syndrome is an autosomal dominant heritable syndrome associated with multiple manifestations. Mutations in the vHL gene can lead to the development of both benign and malignant neoplasms and cysts in a variety of organs including the central nervous system (CNS), kidneys, adrenal glands, endolymphatic sac, epididymus, broad ligament, and pancreas.

The most common pancreatic manifestation of vHL is cystic disease, which can be present in up to 56% of patients.[216,217] Cysts can be single or multiple and can cause symptoms based on compression of contiguous structures such as the stomach or by virtue of their replacement of the pancreas resulting in exocrine insufficiency.[216,217] Solid lesions of the pancreas are manifested by microcystic adenomas as well as pancreatic neuroendocrine tumors.[218] Microcystic adenomas are benign lesions, which in and of themselves do not necessitate treatment. Pancreatic endocrine tumors associated with vHL are encountered in approximately 9% to 12% of patients.[216,217,219] They are by and large nonfunctional tumors. Although there have been sporadic case reports of functional pancreatic neuroendocrine tumors associated with vHL, in a series of approximately 90 patients followed at the National Institutes of Health there have been no examples of functional tumors identified.[216,217,219]

The molecular genetics of the vHL gene are currently under investigation. vHL behaves as a classic tumor suppressor gene and is located on the short arm of chromosome 3 (3p25-26).[220] The majority of patients present with a germ line mutation of the gene from the affected parent and a normal copy of the gene from the unaffected parent. Tumor formation is therefore initiated when both alleles are inactivated usually through a loss of the wild type allele. Such a loss can be the result of a deletion and generally occurs only in susceptible organs. The vHL gene has 3 exons that encode the vHL protein; this protein plays a role in a series of complex binding interactions that mediate the regulation of vascular endothelial growth factor (VEGF). The vHL protein functions in conjunction with hypoxia inducible factors (HIF) 1 and 2 and may exert its effects through these pathways. In addition to VEGF, vHL may also influence the production of platelet-derived growth factor data polypeptide (PDGF data), erythropoietin, and transforming growth factor-alpha (TGF-α).[135,221,222] The regulation of these factors may in part explain the highly vascular nature of tumors associated with the vHL mutations.

The diagnosis of pancreatic neuroendocrine tumors in patients with known or suspected vHL mutations is made through imaging studies since these lesions are almost never associated with symptoms. Although these solid lesions can be detected on a variety of noninvasive imaging techniques such as ultrasound, CT, and MRI, the preferred modality for diagnosis and assessment of size is CT.[216,217,219] Early arterial CT scan is useful not only for discriminating a solid vascular enhancing lesion consistent with a pancreatic neuroendocrine tumor (PNET) but also allows for accurate size measurements to be made which can impact on recommendations for further management. Magnetic resonance imaging

scans, especially T2-weighted images, can be useful in distinguishing a PNET from a microcystic adenoma. Recommendations for screening patients with vHL for the possibility of pancreatic lesions consist of the recommendation of obtaining an abdominal CT in patients with other manifestations of vHL or a known mutation at approximately 15 years of age.[216,217,219] Genetic testing for the disease including qualitative and quantitative southern blotting as well as DNA sequence analyses are now available. Most patients undergoing genetic testing are from known families with a manifestation and the utility of genetic testing helps to confirm the diagnosis to allow for appropriate counseling and directed imaging studies to diagnose manifestations.

The management of pancreatic neuroendocrine tumors arising in the context of vHL is based principally on avoiding metastatic disease. Metastases from primary PNETs in vHL can occur in as many as 12% of individuals with a diagnosed PNET.[216,217] The most common site for metastatic disease is the liver, but lymph nodes and bone can also be involved. The challenge is to determine which patients are at greatest risk for developing metastatic disease and to intervene early with resection of the primary tumor. Since it is exceedingly uncommon (not encountered in the largest series from NIH) to have a functional PNET in the setting of vHL, the management is directed toward preventing the spread of disease. In a review of factors that could potentially influence the risk of developing disseminated disease the size of the primary tumor was the only factor that significantly correlated with this risk.[216,217,220] Although prospective studies are currently under way to evaluate genotype-phenotype relationships as an earlier predictor, these studies are still ongoing. At the present time the recommendation is to resect all lesions larger than 3 cm since these lesions are associated with a significantly increased risk of metastatic disease. For regions of the pancreas such as the pancreatic head or uncinate process where a large lesion may require a more complicated resection such as a pancreaticoduodenectomy, the recommendation is to attempt enucleation for lesions that are 2 cm or larger.[216]

The goal of pancreatic surgery in these patients is to preserve as much of the normal pancreatic tissue as possible. Therefore, pancreatic enucleation is the procedure of choice when possible. However, distal pancreactectomy or pancreacticoduodenectomy is sometimes required to extirpate primary lesions. The operative approach is 1 that is standard to the management of pancreatic neuroendocrine tumors regardless of their origin relying on adequate exposure, inspection, palpation, and intraoperative ultrasound especially to determine the relationship between the

lesions and the pancreatic duct. For those patients with lesions smaller than 2 cm, follow-up surveillance scans at yearly intervals should be performed and any lesion that is increasing in size should be resected. Strategies using minimally invasive approaches such as laparoscopic pancreatic resection are now being utilized more frequently for the management of PNETs associated with vHL.

For the small percentage of patients who do develop metastatic disease these lesions behave in an often indolent fashion. Patients with liver metastasis are often candidates for resection, ablation, or regional treatment strategies.[217] Approximately 50% of patients who develop metastatic disease will succumb to their disease. For patients without evidence of metastatic disease and small (less than 2 cm) lesions in the pancreas that appear stable on serial imaging examinations, the surveillance interval can be expanded to imaging every 2 years. As more information is gathered on genotype and phenotype analysis, revised and refined recommendations for surveillance and management may be possible.

Neurofibromatosis Type 1

von Recklinghausen disease (vRD), or neurofibromatosis type 1 (NF-1), is an autosomal dominant disorder with complete penetrance. It has an incidence of 1 in 3000 live births[135] and is characterized by a constellation of clinical findings. These include benign and malignant central and peripheral nervous system tumors with multiple pigmented and thickened patches of skin (café au lait spots), cutaneous and subcutaneous as well as plexiform neurofibromas, macrochephaly, and other neoplasms.[135,152] Individuals with this disorder have also been noted to have learning disabilities.

Lesions in the duodenum described as carcinoids associated with NF-1 were identified as early as 1970 and appeared in the literature as case reports.[152] Duodenal carcinoids are rare in the general population and represent only 2% of all gastrointestinal carcinoids. Although the exact prevalence of carcinoids in the NF-1 population is not known a variety of case reports indicate the number is higher than the number in sporadic cases.[152] A constellation of findings that include neurofibromatosis, pheochromocytoma, and duodenal neuroendocrine tumors has been described as associated with NF-1. The exact nature of these carcinoids has been studied extensively and it appears that most of them are rich in somatostatin.[220,223,224] The lesions are thought to be primarily composed of cells endocrine differentiation and are regarded as being of low-grade malignant potential.

The duodenal lesions associated with NF-1 are generally detected when they become clinically symptomatic secondary to obstruction. The management of these legions includes local resection as well as more extensive pancreaticoduodenectomy depending on both the size and the location. These lesions tend to be nonfunctional and there is no consequence of their production of somatostatin. Benign cystadenomas of the pancreas have also been described in association with NF-1.[225] Pathologic examination of tissue demonstrates cystic lesions lined with cuboidal epithelial cells with clear cytoplasm consistent with a cystadenoma. Primary adenocarcinomas of the pancreas, duodenum, and small or large bowel have been described in association with vRD.[226,227] However, these cases are rare and most have been diagnosed on the basis of symptoms similar to those of duodenal carcinoids, namely obstruction and bleeding. Rarely, pancreatic neuroendocrine tumors can be present in NF-1. A review of cases has demonstrated a small number of pancreatic malignant neoplasms and an even smaller number of those definitively diagnosed as endocrine malignancies.[203] In short, pancreatic neuroendocrine tumors are a rare manifestation of NF-1. But, when diagnosed, the recommendation is to remove them by surgical resection.

Tuberous Sclerosis

Tuberous sclerosis is an autosomal dominant genetic disorder that affects 1 per 10,000 live births. The underlying genetic abnormality is a mutation in 1 of 2 genes—either TSC 1 or TSC 2. TSC 1 is a gene that encodes the protein hamartin and TSC 2 encodes the protein tuberin. These 2 proteins function together as a tumor suppressor complex and mediate the activity of mTOR. This modulation of mTOR is involved in the regulation of β-catenin stability and activity.[228] Patients suffering from tuberous sclerosis form hamartomas and neoplasms in organs such as the brain, heart, kidney, and skin. In rare cases, they can develop pancreatic neuroendocrine tumors.[228,229] These tumors are generally diagnosed either incidentally or as the result of symptoms due to mass compression or spread. They are rarely functional. These lesions can demonstrate a malignant phenotype and therefore surgical resection at the time of diagnosis is recommended.

Surgical Approaches to Islet Cell Tumors of the Pancreas

The pancreas is located in the retroperitoneal space and this gland is comprised of exocrine and endocrine components, each with distinctive functions. A thorough understanding of pancreatic anatomy is essential to

proper operative decision-making since the relationship of islet cell tumor pathology to the different components of pancreatic anatomy can greatly influence both the operative approach and the extent of resection. The pancreas itself is broadly divided into 4 sections: the head, neck, body, and tail. The head of the pancreas is located on the right side of the abdomen adjacent to the triangle of Calot, whereas the tail of the pancreas is located to the left terminating in the hilum of the spleen. The uncinate process is an important segment of the pancreas that projects from the pancreatic head, extending posteriorly behind the portal vein and superior mesenteric vessels but remaining anterior to the vena cava. Although an infrequent occurrence, islet cell tumors can arise in the uncinate process, a finding that creates difficulty due to the challenging lack of accessibility of the uncinate process.

The pancreas contains a rich ductal system whose primary function is to provide a conduit for exocrine sections into the gastrointestinal tract. The main pancreatic duct traverses each region of the pancreas from the tail to the head, ultimately draining into the second portion of the duodenum at the papilla of Vater (major duodenal papilla). The diameter of the pancreatic duct is smallest in the distal tail and progressively increases as it courses from left to right. The accessory pancreatic duct begins in the neck of the pancreas, arising from the main pancreatic duct and runs in a superior direction to drain into the duodenum at the minor duodenal papilla. Although the pancreatic ductal system has only an exocrine function, the relationship of the pancreatic duct to islet cell tumors impacts decision making (ie, enucleation versus more extensive resection) and the incidence of complications. Pancreatic fistula is 1 of the most frequent complications of pancreatic resection, occurring in 10% to 30% of cases.[230]

A firm understanding of pancreatic vascular anatomy is essential to preoperative and intraoperative decision making. The pancreas is a highly vascular organ that derives its blood supply from the celiac axis and superior mesenteric artery. The head of the pancreas receives its blood supply from the gastroduodenal artery, which branches into the anterior and posterior superior pancreaticoduodenal arteries. Branches from the splenic artery, including the dorsal, transverse, and great pancreatic arteries, provide the blood supply to the body and tail of the pancreas. Venous blood of the pancreas drains into the splenic, mesenteric (both superior and inferior), and portal veins. The splenic vein courses along the dorsal and superior aspect of the pancreas where it unites with the superior mesenteric vein near the pancreatic head to form the portal vein. The proximity of islet cell tumors to these vessels may influence the

surgeon's decision to preserve the spleen during distal pancreatectomy or the feasibility and safety of enucleaction.

Intraoperative Ultrasound. Intraopertive ultrasonography is regarded by many surgeons as an indispensable tool to be used during surgery on the pancreas for an islet cell tumor. It is more sensitive for hepatic metastases than preoperative imaging modalities.

Surgical Technique

Enucleation of Islet Cell Tumors. The abdomen is explored through either a midline or a subcostal incision. The lesser sac is entered by dividing the gastrocolic ligament. The lesion is identified using inspection, bimanual palpation, and intraoperative ultrasound. Using ultrasound, the proximity of the lesion to the main pancreatic duct is assessed. If the duct is a safe distance from what is thought to be a benign tumor, an enucleation can be attempted.

The capsule of the gland overlying the lesion is incised with electrocautery. The tumor is then gently mobilized out of the pancreatic parenchyma using a combination of blunt and sharp dissection. Bipolar electrocautery can be useful for maintaining hemostasis. After hemostasis is confirmed, the operative site is drained.

If the lesion is in close proximity to the main pancreatic duct, or if an injury is suspected during an enucleation procedure, a formal resection should be performed.

Distal Pancreatectomy with Splenectomy. When an open approach is indicated, the operation is typically performed through either a midline, paramedian or subcostal incision. The lesser sac is entered by dividing the gastrocolic ligament. The short gastric vessels are then ligated and divided, separating the spleen for the greater curvature of the stomach. The inferior border of the pancreas is mobilized sharply. The splenic flexure of the colon is released. The surgeon now has 2 options. The first option is to dissect from left to right by first sharply incising the leinorenal ligament. The spleen and the tail of the pancreas are then mobilized out of the retroperitoneum with the splenic artery and vein. The dissection is continued until an oncologically acceptable margin has been obtained proximally. A soft, thin pancreas can then be divided en mass with the splenic vessels using a linear stapler. Fibrotic glands or those with inflammatory changes are better handled by individual ligation of the splenic vessels followed by sharp transection of the pancreas between stay sutures and then oversewing of the pancreatic stump with a nonabsorbable monofilament suture. Individual ligation of the pancreatic duct has not been demonstrated to affect the lateral fistula rate.

The second option it to dissect from right to left. The pancreas is encircled proximal to the lesion taking care not to injure the splenic vein. The gland is then divided either with a linear stapler or sharply as described above. The splenic vessels are ligated and divided. The tail of the pancreas is then mobilized out of the retroperitoneum with the splenic vessels toward the spleen. The leinorenal ligament is incised and the specimen is delivered. Many surgeons elect to place a closed suction catheter in the operative site.

Distal Pancreatectomy with Splenic Preservation. With an open approach, the operation is typically performed through either a midline or subcostal incision. The lesser sac is entered by dividing the gastrocolic ligament. The inferior border of the pancreas is mobilized sharply. The splenic flexure of the colon is released. The splenic artery and vein are identified. The pancreas is encircled proximal to the lesion, taking care not to injure the splenic vein. The gland is then divided either with a linear stapler or sharply between stay sutures. The proximal stump of the pancreas is then oversewn with a nonabsorbable monofilament suture. The distal gland is then dissected out of the retroperitoneum and free from the splenic vessels. During the course of this dissection the surgeon will encounter many small branches of the splenic vein and artery as they enter the pancreas. These can be controlled with either fine monofilament sutures or small clips. Many surgeons elect to place a closed suction catheter in the operative site.

Central Pancreatectomy. The abdomen is explored through an upper midline incision. The lesser sac is entered by dividing the gastrocolic ligament. The location of the lesion within the neck of the pancreas is confirmed by inspection, palpation, and intraopertive ultrasonography. The inferior border of the pancreas is mobilized free from the retroperitoneum. The neck of the pancreas is encircled, taking care not to injure the splenic vessels. The pancreas is then transected either sharply between stay sutures or with a linear stapler to the right of the lesion. The pancreas with the lesion is then dissected free from the splenic vessels, from right to left toward the spleen. During the course of this dissection, multiple small branches of the splenic vessels must be ligated as they enter the specimen. Once a safe margin has been obtained, the distal pancreas is divided sharply between stay sutures. An additional 2 cm of pancreatic body are dissected free from the splenic vessels in preparation for reconstruction. The distal pancreas can be drained into either the stomach (pancreaticogastrostomy) or into the small bowel (pancreaticojejunostomy). For a pancreaticogastrostomy, the posterior wall of the body of the stomach is brought into apposition with the cut edge of the distal

pancreas. A gastrostomy is made in the posterior wall of the stomach. An end-to-side anastamosis is performed in 2 layers with interrupted silk and running absorbable monofilament sutures. For pancreaticojejunostomy, a roux-en-Y is created approximately 40 cm distal to the ligament of Treitz. An end-to-side pancreaticojejunostomy is performed in 2 layers with interrupted silk and continuous absorbable monofilament sutures. Many surgeons elect to place a closed suction catheter in the operative site.

Pancreaticoduodenectomy. The abdomen is explored through an upper midline or bilateral subcostal incision. The abdomen is inspected for evidence of metastatic disease. Each of the 8 segments of the liver are scanned with the intraoperative ultrasound probe. In the absence of metastatic disease, resectabilty is assessed. The hepatic flexure of the colon is sharply incised. The duodenum is widely mobilized to the ligament of Treitz, using a Kocher maneuver. The gastrocolic ligament is divided, and the lesser sac is entered. The transverse colon and its mesentery are then dissected free from the duodenum and the head of the pancreas. The superior mesenteric vein is identified and traced cephelad under the neck of the pancreas. During this dissection, the middle colic vein and the gastroepiploic vein will be identified entering the superior mesenteric vein.

The gallbladder is then dissected free from the gallbladder fossa in a retrograde fashion. The structures of the triangle of Calot are dissected. The cystic artery and duct are identified, ligated, and divided. The hepatoduodenal ligament is then sharply dissected. The hepatic artery is identified and traced to the gastroduodenal artery (GDA). The GDA is occluded with a vascular clamp and the surgeon palpates for a pulse in the right hepatic artery. This confirms the identity of the GDA and avoids inadvertent ligation of the common hepatic artery. Once properly identified, the GDA is ligated and divided. The portal vein is identified in the space between the common bile duct and the common hepatic artery, posterior to the GDA. The portal vein is dissected caudally, under the neck of the pancreas completing the tunnel. The surgeon then palpates the superior meseteric artery and the tumor to ensure that there is a plane of soft tissue between them. After these maneuvers, resectability has been confirmed.

The surgeon palpates the posterior lateral aspect of the bile duct in search of a replaced right hepatic artery. The blood supply to the bile duct depends heavily on this vessel, which should be preserved when present, to help prevent biliary-enteric anastomotic complications.

The bile duct is divided sharply. The stomach is divided with a linear stapler. In a pylorus-sparing pancreaticoduodenectomy, the duodenum is

divided just distal to the pylorus. The jejunum is divided with a linear stapler approximately 10 cm distal to the ligament of Treitz. The blood supply to the very proximal jejunum and the 4th portion of the duodenum is divided between clamps and silk ties. This portion of the bowel is then passed under the root of the small bowel mesentery into the right upper quadrant. Stay sutures are placed in the neck of the pancreas to control the transverse pancreatic artery. The neck of the pancreas is then divided sharply between the stay sutures. Individual bleeding points on the cut surface of the pancreas are controlled with suture ligatures. This leaves the uncinate process attached to the superior mesenteric artery.

The portal/superior mesenteric vein is rolled to the left exposing the superior mesenteric artery. The gland is dissected free from the artery between clamps and heavy silk ties. Some surgeons elect to control this vascular pedicle with a linear stapling device. Once hemostasis is achieved, and negative margins have been confirmed by frozen section, the reconstruction is performed.

The jejunum is brought into the right upper quadrant through a defect that is created in the transverse mesocolon just to the right of the middle colic vessels. It is not brought in to the upper abdomen through the space created during the resection at the ligament of Treitz, because local recurrence in this area is common and would obstruct the biliary, pancreatic, and gastrointestinal reconstructions simultaneously. An end-to-side pancreaticojejunostomy is created in 2 layers with interrupted silk and continuous monofilament sutures. Some surgeons prefer an anastomosis of the pancreatic duct directly to the jejunal mucosa. Several centimeters distal to this, an end-to-side choledochojejunostomy is performed. Large bile ducts can be sewn in a continuous fashion. Normal sized bile ducts, however, should be reconstructed with interrupted absorbable monofilament sutures. Approximately 10 cm distal to this, the gastrojejunostomy (or duodenojejunostomy in the case of a pylorus-sparing pancreaticoduodenectomy) is performed in an end-to-side fashion with a single layer of continuous monofilament sutures. Many surgeons elect to drain the operative site and some place a gastrostomy tube to aid in the postoperative recovery.

Total Pancreatectomy. Total pancreatectomy has a real but limited role in the armamentarium of pancreatic surgeons. Indications for total pancreatectomy are narrow and include failure of medical therapy in select cases of chronic pancreatitis and for multifocal pancreatic cancer that is potentially curable by surgery. The abdomen is explored either through an upper midline or bilateral subcostal incision. The abdomen is inspected for evidence of metastatic disease. Each of the 8 segments of

the liver are scanned with the intraoperative ultrasound probe. In the absence of metastatic disease, resectabilty is assessed. The hepatic flexure of the colon is sharply incised. The duodenum is widely mobilized to the ligament of Treitz, using a Kocher maneuver. The gastrocolic ligament is divided, and the lesser sac is entered. The transverse colon and its mesentery are then dissected free from the duodenum and the head of the pancreas. The superior mesenteric vein is identified and traced cephalad under the neck of the pancreas. During this dissection, the middle colic vein and the gastroepiploic vein will be identified entering the mesenteric vein. These vessels can be ligated.

The gallbladder is then dissected free from the gallbladder fossa in a retrograde fashion. The structures of the triangle of Calot are dissected. The cystic artery and duct are identified, ligated, and divided. The hepatoduodenal ligament is then sharply dissected. The hepatic artery is identified and traced to the gastroduodenal artery (GDA). The GDA is occluded with a vascular clamp and the surgeon palpates for a pulse in the right hepatic artery. This confirms the identity of the GDA and avoids inadvertent ligation of the common hepatic artery. Once properly identified, the GDA is ligated and divided. The portal vein is identified in the space between the common bile duct and the common hepatic artery, posterior to the GDA. The portal vein is dissected caudally, under the neck of the pancreas completing the tunnel. The surgeon then palpates the superior mesenteric artery and the tumor to ensure that there is a plane of soft tissue between them. After these maneuvers, resectability has been confirmed.

The surgeon palpates the posteriolateral aspect of the bile duct in search of a replaced right hepatic artery. The blood supply to the bile duct depends heavily on this vessel, which should be preserved to help prevent biliary enteric anastomotic complications.

The bile duct is divided sharply. The stomach is divided with a linear stapler. In a pylorus-sparing pancreaticoduodenectomy, the duodenum is divided with a linear stapler just distal to the pylorus. The jejunum is divided with a linear stapler approximately 10 cm distal to the ligament of Treitz. The blood supply to the very proximal jejunum and the 4th portion of the duodenum is divided between clamps and silk ties. This portion of the bowel is then passed under the root of the small bowel mesentery into the right upper quadrant.

The inferior border of the pancreas is mobilized out of the retroperitoneum. The splenic flexure of the colon is released. The short gastric vessels are ligated and divided. The leinorenal ligament is divided sharply and the spleen is mobilized out of the retroperitoneum with the tail of the

pancreas. This dissection is continued to the neck of the gland, at which point the splenic vessels are individually ligated and divided. This leaves the uncinate process attached to the superior mesenteric artery.

The portal/superior mesenteric vein is rolled to the left exposing the superior mesenteric artery. The gland is dissected free from the artery between clamps and heavy silk ties. Some surgeons elect to control this vascular pedicle with a linear stapling device. Once hemostasis is achieved, and negative margins have been confirmed by frozen section, the reconstruction is performed.

The jejunum is brought into the right upper quadrant through a defect that is created in the transverse mesocolon just to the right of the middle colic vessels. An end-to-side choledochojejunostomy is performed. Large bile ducts can be sewn in a continuous fashion. Normal sized bile ducts, however, should be reconstructed with interrupted absorbable monofilament sutures. Approximately 10 cm distal to this, the gastrojejunostomy (or duodenojejunostomy in the case of a pylorus-sparing pancreaticoduodenectomy) is performed in an end-to-side fashion with a single layer of continuous monofilament sutures. Most surgeons elect to drain the operative site and some place a gastrostomy tube to aid in the postoperative recovery.

Laparoscopic Pancreatic Surgery. Despite the many advances in laparoscopic techniques during the 1990s, laparoscopic pancreatic surgery (Fig 10) has not experienced the widespread applicability compared with other advanced laparoscopic procedures such as laparoscopic adrenalectomy or gastric bypass. Many of the initial publications on laparoscopic pancreatic surgery are case reports or small case series. Since 2000, however, there has been a dramatic increase not only in the number of publications but also in the complexity of the operative procedures. Almost all open pancreatic resection techniques have now been performed laparoscopically. Although there have been no randomized controlled trials of laparoscopic versus open pancreatectomy, the outcome and complication rate of laparoscopic pancreatic resection appears equal to or better than that of open surgery.[231] Moreover, a laparoscopic approach leads to less pain and a shorter hospital stay.[232]

Patient positioning depends on the type of pancreatic resection that is being undertaken and the preference of the surgeon. For most laparoscopic pancreatic procedures, the patient is placed in the modified lithotomy position with the legs in a split but straight position. Great care is taken to pad all pressure points. Stirrups should be avoided since the true lithotomy position can lead to neuropraxia especially if a long operative time is anticipated. A small bolster is placed under the left flank

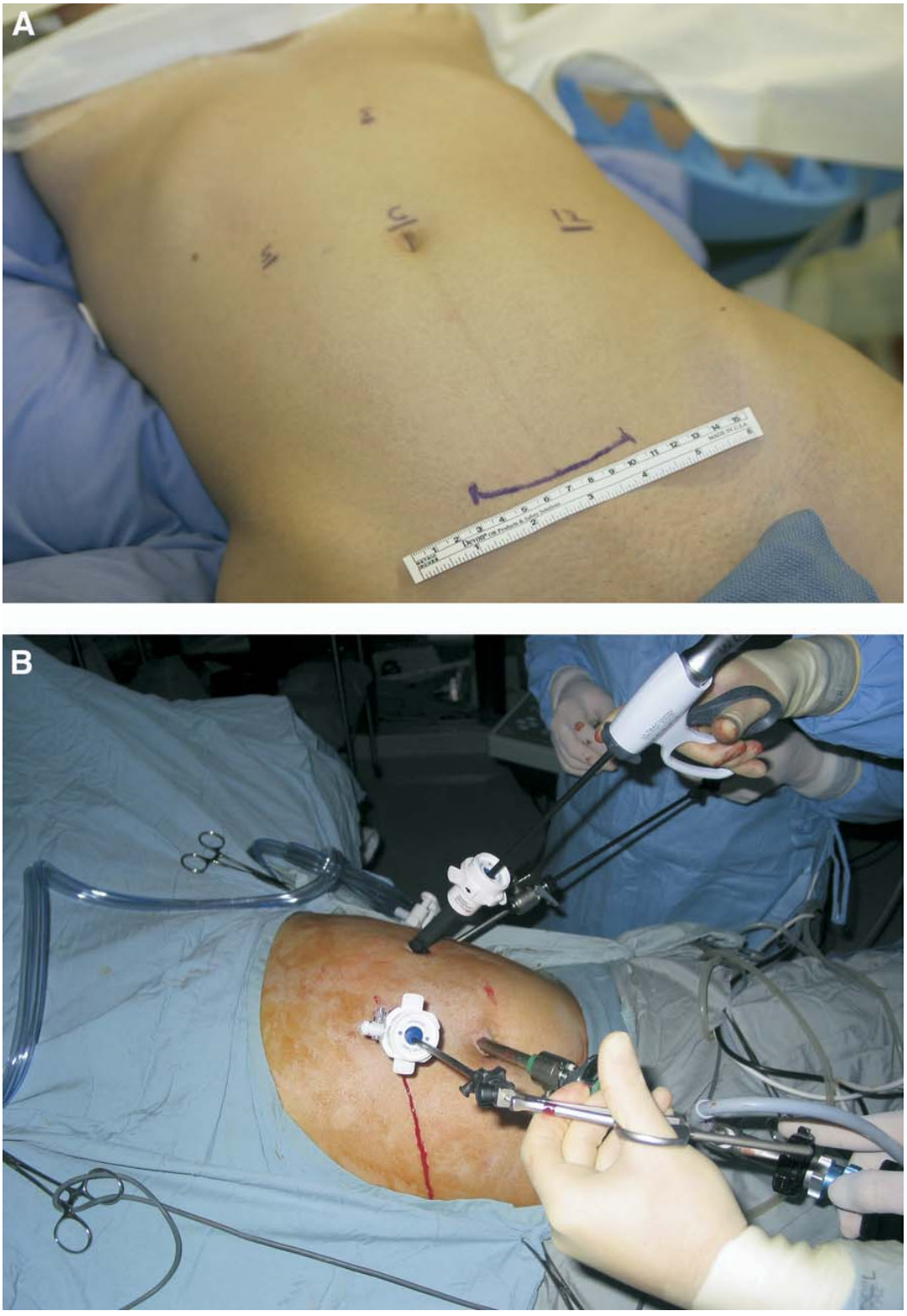

FIG 10. This series of photographs depicts the conduct of a laparocopic resection of an insulinoma. The incisions are planned for a hand-assist procedure with the hand port low in the abdomen (A) in this case. If the patient is in a decubitus position for a lesion in the tail, an upper abdominal hand port site may be preferable. The operation is started with laparoscopic instrumentation without the hand inserted (B) to take down the short gastric vessels and enter the lesser omental sac so the pancreas can be exposed (C). An insulinoma is identified within the neck of the pancreas (D) and is enucleated (E). The postoperative appearance of the scars is excellent (F). (Color version of figure is available online.)

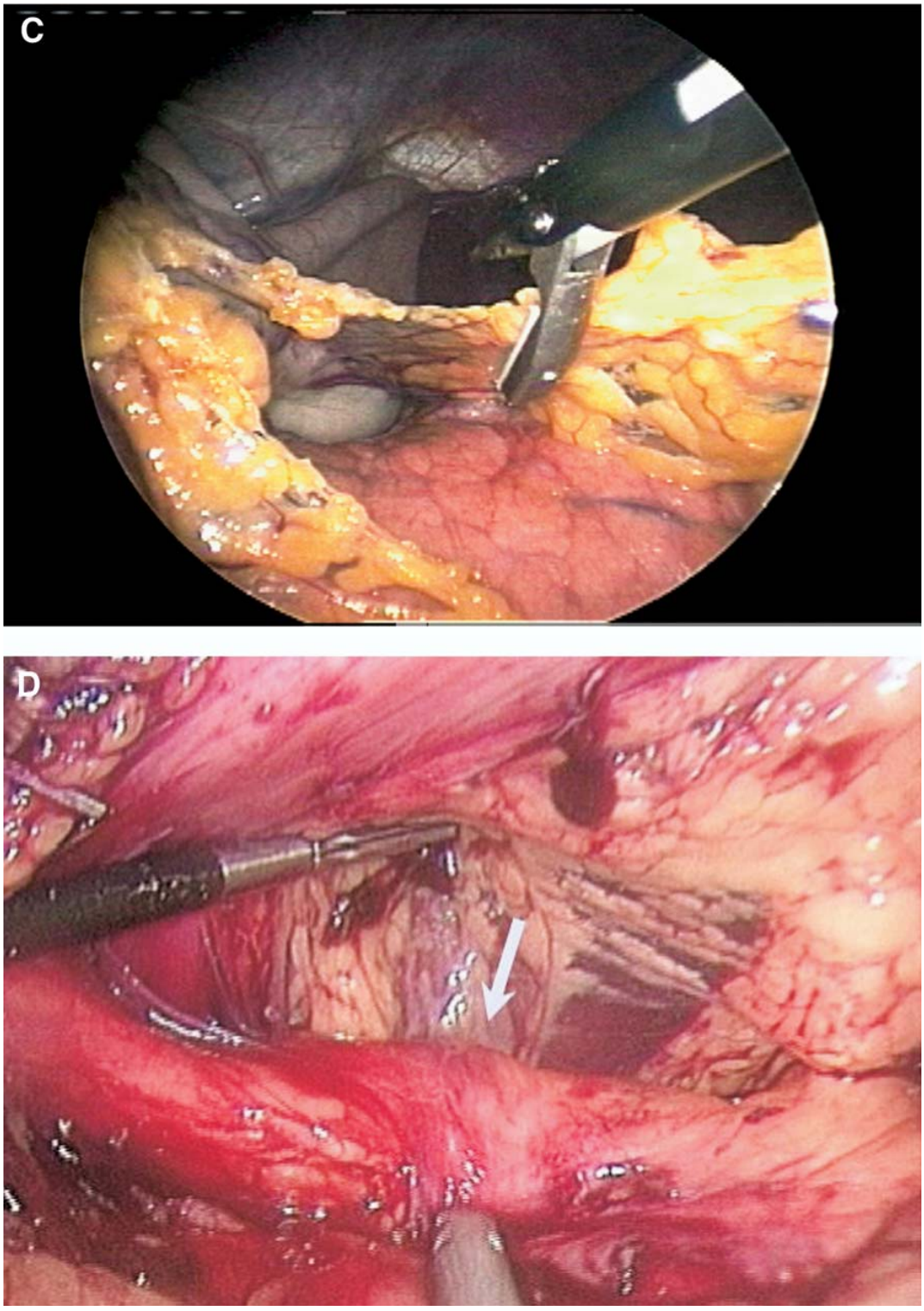

FIG 10. Continued

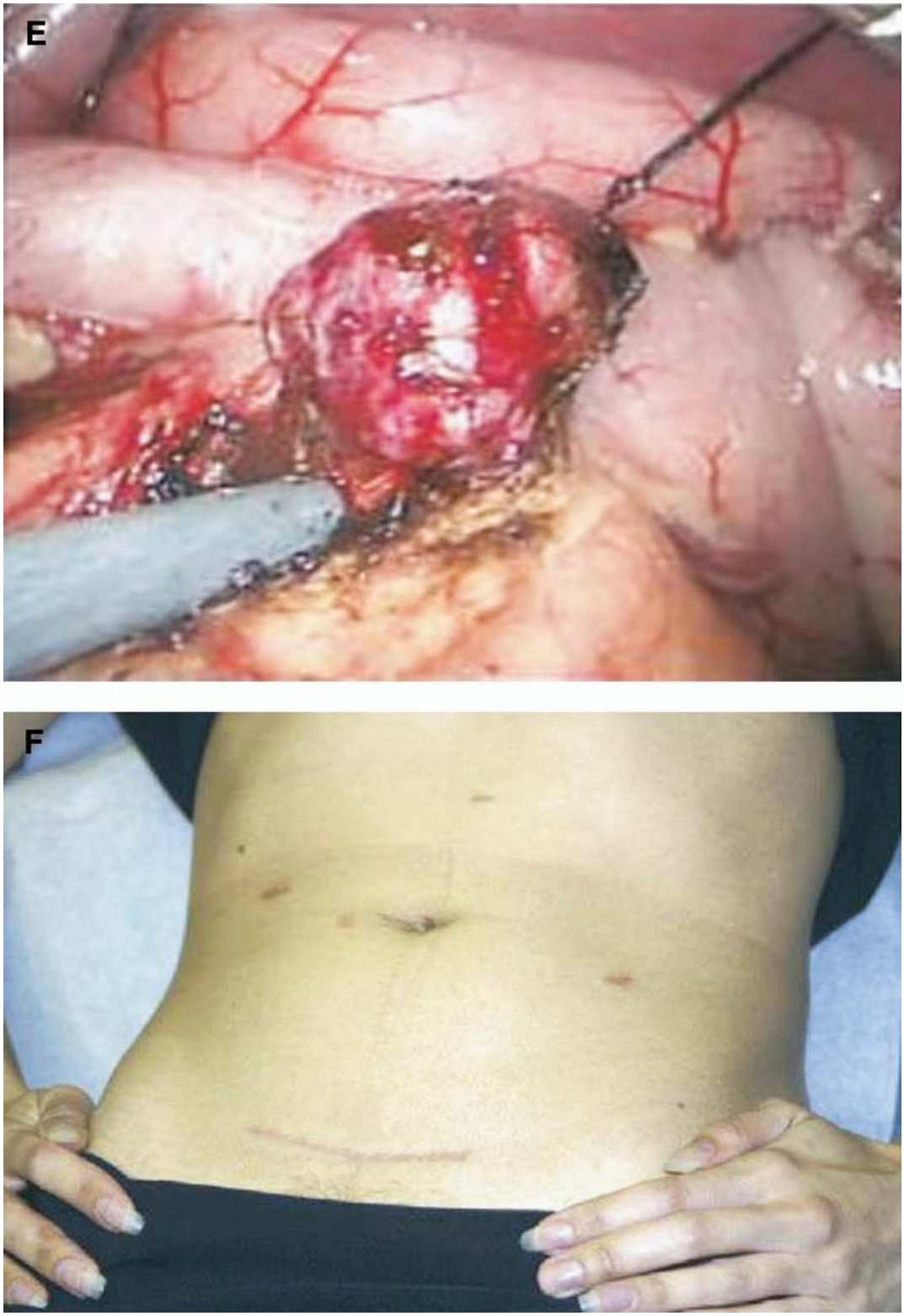

FIG 10. Continued

and the operating surgeon stands between the legs. The modified lithotomy position allows the surgeon to work in the upper abdomen in an ergonomically friendly configuration. By elevating the left side with a bolster, the patient can be placed in either the supine or decubitus position by tilting the table. Alternatively, for laparoscopic distal pancreatic procedures, the patient can be placed in the lateral decubitus position similar to that for laparoscopic left adrenalectomy or splenectomy.

A closed or open technique can be used to enter the abdomen depending on surgeon preference and pneumoperitoneum is achieved by insufflating carbon dioxide to 15 mm Hg. An angled 30 degree 10 mm endoscope is used for most cases. Two upper abdominal 12-mm working trocars are used (1 on the left and 1 on the right), either of which can accommodate a linear stapler and/or the laparoscopic ultrasound probe. A 5-mm epigastric trocar is inserted to permit anterior retraction of the stomach and a left lateral trocar is inserted for 1 of the assistants. Almost all procedures begin by dividing the short gastric vessels with either the Ligasure™ (Valleylab, Boulder, CO) or an ultrasonic scalpel to expose the anterior surface of the pancreas. Laparoscopic ultrasound is then performed to assess the anatomy of the lesion. Features such as size, location, proximity to the pancreatic duct, splenic hilum, and splenic vessels are assessed by ultrasound to determine the type of resection to be performed.

Enucleation is the preferred technique for most benign-appearing islet cell tumors; however, if the lesion is large or located near the pancreatic duct (as determined by preoperative studies or intraoperative ultrasound), laparoscopic distal pancreatectomy with splenic preservation is preferred. Laparoscopic enucleation is performed using small spatulated instruments and the hook or spatula electrocautery to carefully excise the islet cell tumor. The capsule of the lesion must not be violated so often an "endopeanut" is used to retract the lesion. Occasionally a retracting suture is placed in the lesion using intracorporeal suturing techniques. The suture can then be used to elevate and retract the islet cell tumor. If the correct dissection plane is maintained, bleeding should be minimal. A closed suction drain is inserted once enucleation has been completed.

Laparoscopic distal pancreatectomy is performed in the same manner as that described in the open section. If splenic preservation is deemed feasible, the surgeon has 2 choices. The first technique is to mobilize the pancreas from the splenic vessels using small clips and/or sutures. The second option involves dividing the splenic vessels proximally and again distally in the hilum of the spleen.[233] With the latter technique, the blood supply to the spleen is based on the short gastric vessels, so several of

these vessels must be preserved during mobilization of the greater curvature of the stomach. Finally, the feasibility of laparoscopic central pancreatectomy and pancreatoduodenectomy has been demonstrated but the benefit of a laparoscopic Whipple has been questioned.[234,235]

Complications

Although the mortality rate after pancreatic surgery has been reduced recently, the rate of postoperative complications is still high. One of the most common complications following pancreatectomy is pancreatic fistula.[236] The group at Johns Hopkins has reported a fistula rate of 11.4% following pancreaticoduodenectomy, and this rate does not seem to vary between different operative techniques.[237]

It has been reported that the rate of pancreatic fistula after central pancreatectomy with pancreaticojejunostomy is 36%. Fistula formation can be managed conservatively with drainage and almost always resolves within 1 month.[238] Several surgical techniques and devices had been proposed to facilitate fistula closure, such as the use of fibrin-glue sealing, stapler closure, an ultrasonic dissector, or an ultrasonically activated scalpel to prevent pancreatic fistula, although none are proven.[236]

Complications occurred in 43% of patients after pancreaticoduodenectomy (the University of Indiana, 20-year experience), including cardiopulmonary events (15%), fistula (9%), delayed gastric emptying (7%), and sepsis (6%). Perioperative mortality was 3.9% overall.[239]

Hemorrhage several days following pancreatic surgery is potentially a catastrophic complication. This occurs most commonly in patients with preceding intra-abdominal complications such as pancreatic fistula, biliary fistula, and intra-abdominal abscess.[240] The mortality rate in patients with delayed hemorrhage is 18%.[241] Among other complications of pancreatectomy with pancreatico-enteric anastomosis are upper gastrointestinal bleeding and small bowel obstruction and they are relatively rare (1% to 2%). Approximately 15% of patients after pancreaticoduodenectomy may experience delayed gastric emptying, which eventually resolves but often delays discharge for the patients.[242] Total pancreatectomy results in endocrine (insulin-dependent diabetes mellitus) and exocrine insufficiency and requires insulin and enzyme supplementation.

Conclusion. There is a wide array of surgical options available to the pancreatic surgeon. Careful preoperative evaluation with appropriate diagnostic and imaging tests facilitate operative decision making. Surgeons should be familiar with all of the different operative techniques so that decisions can be individualized to optimize patient care.

Islet Cell Cancers: Treatment of Metastatic Disease

Resection of Metastatic Disease

The first option for treatment of limited metastatic disease is resection, provided the patient poses a satisfactory risk for such an operation. Historical reports of patients with metastatic neuroendocrine tumors suggest a relatively indolent course, but the 5-year survival rate for patients not treated by resection is 20% to 30%.[243,244] Improved safety and reduced morbidity and mortality rates associated with liver resection in the current era justifies surgery for palliation of symptoms.[245,246] The suggestion, however, that survival is prolonged in asymptomatic patients is not unassailable. There are only retrospective nonrandomized reports to support this assertion.

Undoubtedly, hepatic resection can provide symptomatic relief of endocrine hormone excess. The patients who benefit the most from resection of hepatic metastases are those who have symptomatic and limited disease and for whom resection is performed with the intention of removing all visible disease. In a series of 85 patients with neuroendocrine hepatic metastases referred to Memorial Sloan-Kettering Cancer Center, 34 were deemed candidates for resection.[247] Of these, 21 (62%) had bilobar disease. The nonsurgical patients were treated medically or with chemoembolization. Relief of hormonal symptoms was accomplished reliably with either resection (13 of 13 patients) or chemoembolization (15 of 16 patients). Surgical cure was the intent for 28 of the 34 patients, but complete resection of metastases was possible in only 15 (44%). In this series, the median survival for all patients was more than 5 years with a 5-year survival rate of 53%. The only factor associated with the best outcome by multivariate analysis was curative intent of treatment. The 5-year survival rate for surgically treated patients was 76%, while no patient relegated to medical treatment only survived for 5 years. The group at Northwestern University has recently reported their series of 36 patients with liver metastases from neuroendocrine tumors.[248] Sixteen patients underwent liver resection and 20 were treated with chemoembolization. The median survival rate for patients who underwent operation was not reached after a median observation interval of 30 months and the actuarial 5-year survival rate was 70%. Among the 16 patients undergoing resection, the best survival was noted in patients who had previously undergone resection of the primary tumor or who had 4 or fewer metastases resected. For the patients treated with chemoembolization, the median survival was 32 months and the 5-year survival was 40%. Another

recent report from MD Anderson Cancer Center examined their series of 163 patients with nonfunctioning neuroendocrine pancreatic cancers treated between 1988 and 1999.[249] Overall median survival was 3.2 years for the group and 2.2 years for those with metastatic disease at the time of presentation. Complete resection of the primary tumor and all apparent metastases was possible for only 4 patients. These 4 patients are all alive at a median of 4 years but developed additional metachronous liver metastases at a median of 1.4 years. No survival benefit was associated with resection of the primary tumor in the presence of unresectable metastases. Resection of a primary tumor in the presence of unresectable metastatic disease should be limited to the palliation of significant symptoms such as gastrointestinal bleeding.

In 1 retrospective review encompassing a 15-year period and 60 patients with metastatic neuroendocrine tumors including carcinoids and islet cell cancers, the group at the Medical College of Wisconsin found patients who underwent aggressive surgical resection and ablation of hepatic metastases were more likely to have symptom relief and improved survival compared with patients who have medical treatment alone ($P < 0.05$).[250] In this series, patients were stratified as to whether more than 50% of the liver was involved. This subset of patients fared significantly worse with a 5-year survival rate of only 8% compared with a 5-year survival rate of 67% if less than 50% of the liver was involved.

Radiofrequency Ablation

The use of thermal tissue ablation for tumor debulking may be a option, particularly in those patients who are not candidates for more extensive operation or resection. Ablative modalities, particularly radiofrequency ablation (RFA) but also cryotherapy, have garnered favor to treat liver metastases from a variety of tumors. Radiofrequency ablation has been shown to be effective in local control of disease in patients with hepatocellular carcinoma as well as metatases from colorectal carcinoma, melanoma, and sarcoma.[251-255] It has also been used in the treatment of hepatic metastases from neuroendocrine tumors.[254-258] Radiofrequency ablation may be a particularly useful modality for patients with multifocal functional endocrine metastases, because the goal of cytoreduction with relief of symptoms due to hormone excess is achievable with less morbidity than is associated with extensive liver resections. Furthermore, some series have shown that RFA is applicable, in the setting of limited metastatic disease, percutaneously or via the laparoscope under ultrasound guidance (Fig 11). In a report of their 5-year experience with laparoscopic RFA in the treatment of hepatic neuroendocrine metastases,

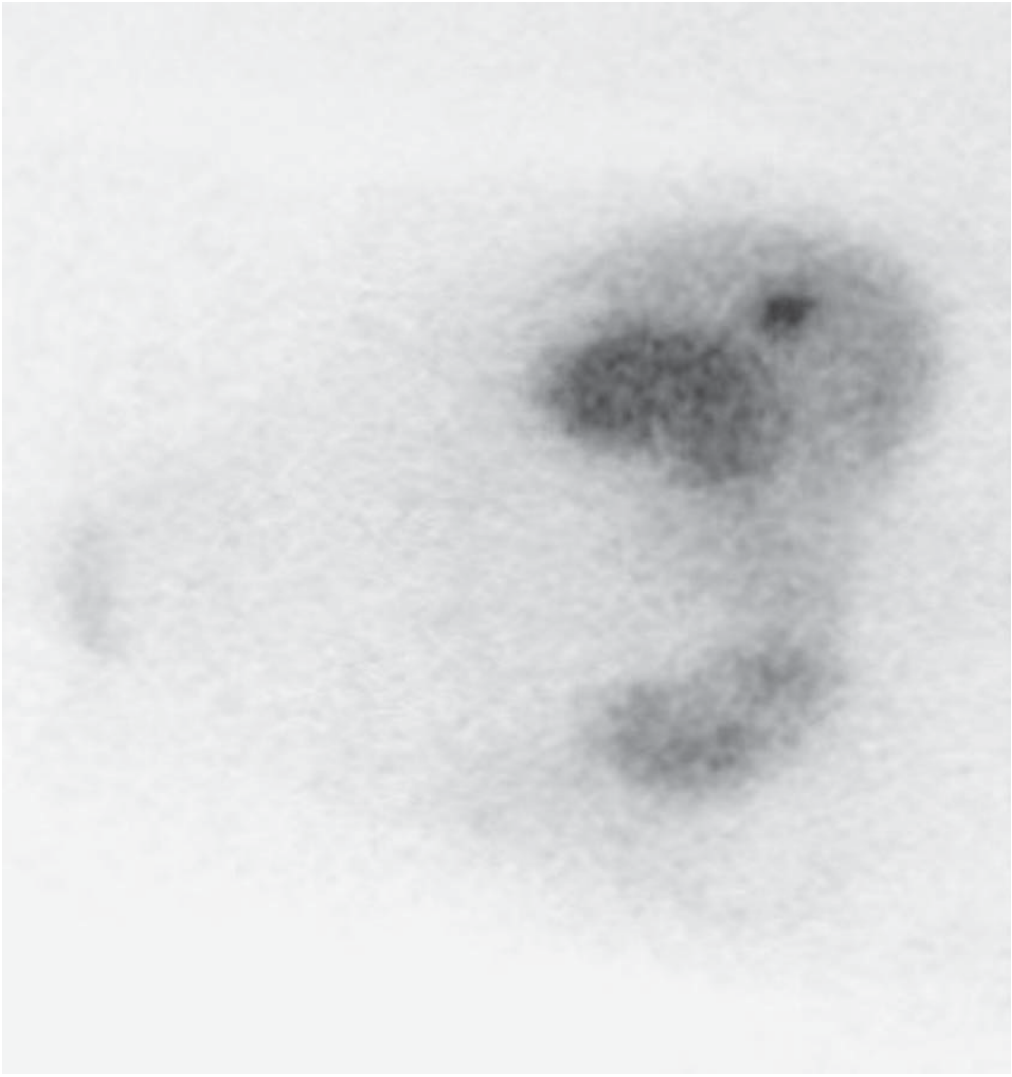

FIG 11. This solitary liver metastasis of a nonfunctioning islet cell cancer was detected by somatostatin receptor imaging. It was treated by percutaneous radiofrequency ablation under CT guidance.

Berber and colleagues reported that symptoms were ameliorated in 95% of patients with significant or complete symptom control in 80% of patients for a mean of 10 months (range 6 to 24 months).[256] Sixty-five percent of patients demonstrated a partial or significant decrease in their tumor markers. The largest reported series using cryotherapy is by Seifert and colleagues.[259] These authors treated 52 lesions in 13 patients. In the 7 patients with endocrine symptoms, complete and partial improvement was seen in 5 and 2 patients, respectively. Only 3 patients were evaluated with hormone serum level assay, but all showed a marked decrease in levels. After a median follow-up interval of 13.5 months, 12 patients were still alive, with 2 having recurrent disease in the liver. A limiting concern

is the high complication rate of 31% including coagulopathy and bleeding, acute renal failure, and pulmonary embolism. A reported advantage of RFA is a lower risk of complications. In the series by Siperstein and Berber,[260] 115 lesions in 18 patients with neuroendocrine liver metastases were treated with laparoscopic RFA. They followed 15 of the patients for a mean of 12 months. Three of the patients died and local recurrence was reported in an additional 3 patients. They had 2 complications. One patient had postoperative atrial fibrillation and 1 had upper gastrointestinal bleeding. Most were discharged within 24 hours of surgery.

Liver Transplantation

The experience with transplantation is limited, but liver transplantation is occasionally appropriate for patients with extensive symptomatic liver metastases in the absence of distant disease. Proponents argue that for these patients, liver transplantion provides relief of symptoms related to hormone excess. In the largest series, which is a report of the multicenter French experience, the 5-year actuarial survival was 36% with 5 patients surviving more than 5 years.[261] It is notable that these patients had already failed other treatments. Only 16% of their 31 patients had not undergone any prior medical or surgical treatment. The high operative mortality of 19%, however, suggests that transplantation should be used only for carefully selected patients. In this series, patients with carcinoid tumors fared better than those with other neuroendocrine cancers, but this is not a universal finding in other single institution series. The limited supply of donor livers will limit the use of transplantation in these patients since they are often not high enough on an institution's priority list to get an organ.

Hepatic Artery Infusional Treatments

Hepatic artery embolization and chemoembolization are other options for patients with symptomatic metastatic islet cell tumors that have failed more conservative therapies (Fig 12). Hepatic artery chemoembolization is a potentially useful modality for patients not eligible for resection or ablative treatment. It is known that the blood supply to neuroendocrine tumor hepatic metastases is derived from the hepatic artery, whereas normal hepatic tissue is preferentially supplied by the portal venous system. Although chemoembolization seems the prevalent modality presently, it is not clear that the addition of chemotherapy to hepatic artery ligation or embolization adds survival benefit because this issue has not been resolved by a clinical trial. Similarly, the optimal chemotherapy

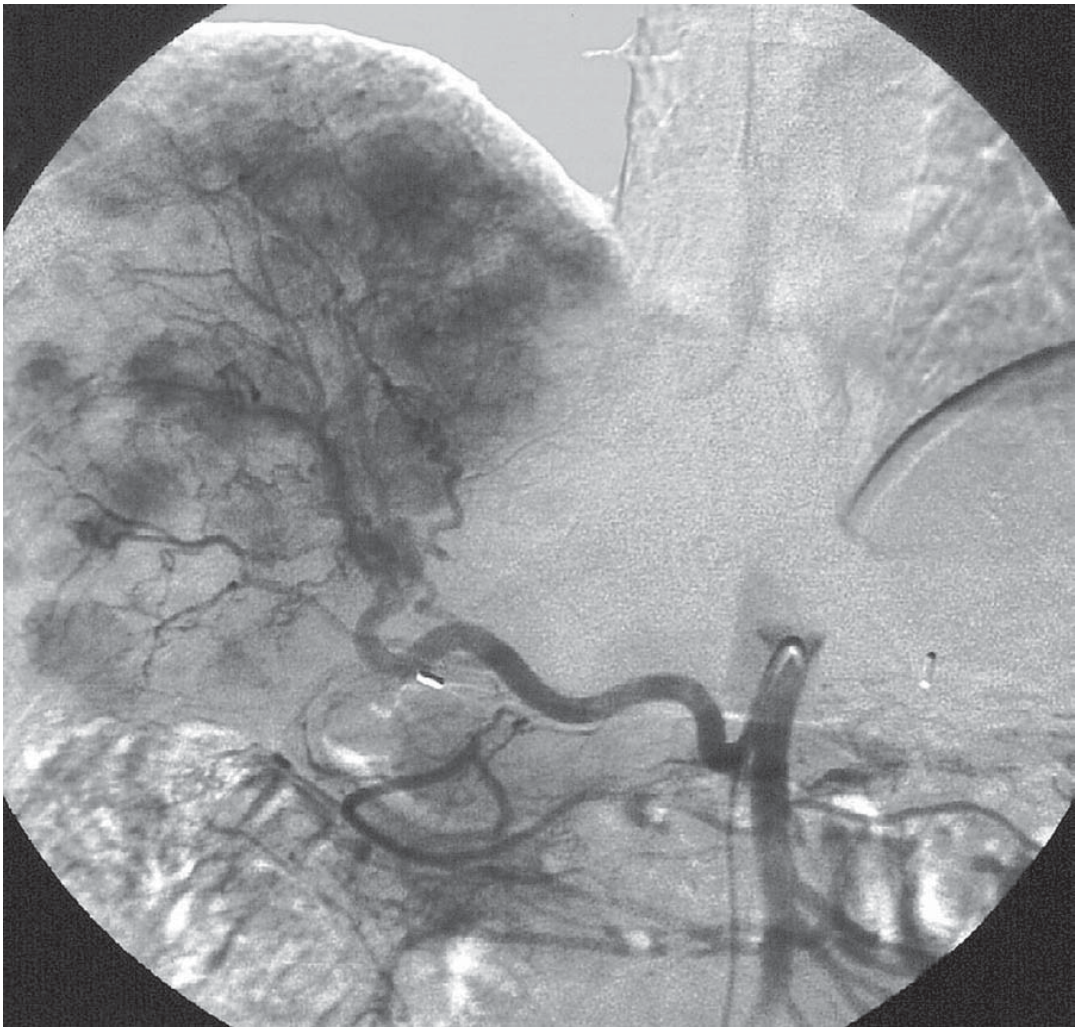

FIG 12. Angiogram demonstrates a large metastasis of a PTH related peptide-producing islet cell cancer. This patient's symptomatic hypercalcemia has been controlled with periodic chemoembolization of the multiple liver metastases.

regimen has not been studied and some data are extrapolated from the treatment of primary hepatic tumors. Our protocol is the same as that used by the Northwestern group[248] employing cisplatin, doxorubicin, and mitomycin C. It is often associated with marked improvement in either hormonal symptoms or pain, and in anecdotal experience, occasional long-term survival. Hepatic arterial embolization, whereby thrombogenic material such as gelfoam is injected into the hepatic artery, has been shown to be effective in treating the hormonal syndromes and local symptoms related to the hepatic metastases.[262] Hepatic artery chemoembolization is a similar procedure that involves the administration of cytotoxic chemotherapeutic agents mixed with conventional thrombogenic agents. Studies using emulsified doxorubicin[263-265]or microencap-

sulated cisplatin[266] have reported decreased hormone secretion, relief of symptoms, and a decrease in average tumor size in small series of patients. Transient abdominal pain, fever, and increases in hepatic enzyme levels are common.[267] Infection, bleeding, myocardial infarction, stroke, renal failure, ileus, and acute gangrenous cholecystitis have all been reported following chemoembolization.[262] In addition, treatment-related mortality has been reported to range from 2% to 5%.[262] The use of embolization or chemoembolization as a palliative modality to treat patients with symptomatic refractory disease may delay the need to institute systemic chemotherapy.

Chemotherapy

Somatostatin Analogues

Somatostatin is a naturally occurring peptide that has an inhibitory function in the gastrointestinal tract and pancreas. Octreotide is an 8-amino-acid analogue of the naturally occurring gut hormone somatostatin. Its activity is mediated through 5 currently known somatostatin-membrane bound receptors. The effect of somatostatin on the target digestive organs mediated by receptors types 2 and 5 (SSTR2 and SSTR5) include antimitotic effects.[268] There is some rationale for treatment of endocrine cancers with octreotide because these cells generally harbor high levels of membrane receptors to somatostatin.[269] SSTR2 and SSTR5 are present in 90% and 80% of pancreatic endocrine tumors, respectively,[270] and Kvols and colleagues observed that the response to octreotide correlates with the presence of receptors.[271] Octreotide is cytostatic to many types of tumor cells in vitro,[272] but the effect has not translated to the clinic. Occasional regression of tumor or inhibition of growth has been reported with octreotide treatment, but a durable response is rare. Furthermore, liver metastases may undergo infarction spontaneously thus confusing interpretation of the response seen.[273] Octreotide has a longer half-life than the naturally occurring peptide (2 hours after intravenous infusion versus less than 3 minutes). Octreotide is therefore more therapeutically relevant and can be used in patients with metastatic neuroendocrine tumors to reduce hormone secretion and neoplastic proliferation.[262] Patients who have poorly controlled hormonal symptoms or rapidly progressive tumors are treated with 150 to 1500 μg daily of octreotide in 3 divided doses that are administered subcutaneously. Patients who are going to respond to treatment do so rapidly, often with symptomatic improvement within hours after the first injection. In those who do not show a clinical

response, the dose should be escalated, and if no therapeutic benefit is seen at this higher dose then this course of therapy is not likely to be effective and should be discontinued.[262] Most authors report a response to octreotide on the basis of either an improvement of hormone-related symptoms or a greater than 50% reduction in serum hormone levels. Using these criteria, 60% to 80% of patients will have a positive response when treated with octreotide.[274,275] The responsiveness of octreotide is known to correlate with the expression of somatostatin receptors on the tumor surface.[260] The overall duration of response can range from weeks to years although almost all tumors will eventually become refractory to octreotide.[276] In addition to causing decreased hormonal production and symptomatic relief in most cases, somatostatin analogues have also been shown to have an antitumor response with studies showing tumor stabilization and some responders with a decrease in tumor size. Studies vary with respect to the length of time the antitumor response persists.[277-279] In 1999, a long-acting release (LAR) formulation of octreotide became available. This preparation was compared with standard octreotide therapy in patients with carcinoid tumors and was found to be equally effective in managing symptoms and tumor progression.[280] Patients who tolerate a trial of the short-acting regimen can be changed to the LAR formulation at a dose of 30 mg once per month. Therapeutic levels are not reliably reached for the first 2 months after the initial LAR injection and therefore standard octreotide injections may be needed during this time to maintain hormonal control.[264,266]

Interferon

Interferon-α has been studied alone or in combination for the treatment of islet cell cancers. One multicenter Italian study[281] is often quoted to show efficacy of interferon-α in patients with neuroendocrine tumors. In this study, interferon-α2a as used was associated with partial or complete remission of carcinoid symptoms in 64% of patients but had little activity on the growth of tumors. But this study population of 53 patients included only 4 who had islet cell cancers. A German study[282] of 25 evaluable patients with progressive neuroendocrine tumors treated with interferon-α2b similarly showed control of symptoms in 66% of their patients. Although tumor regression was seen in patients with carcinoid tumors, no objective tumor regression was seen in patients with pancreatic endocrine cancers. The median time to progression in this study was 34 weeks and did not differ significantly between pancreatic endocrine and carcinoid tumors. So, although tumor regression is unlikely as a result, treatment

with interferon-α may help control symptoms of peptide excess in some patients but in general octreotide has fewer side effects.[283]

Some authors[284] have studied the combination of lanreotide and interferon-α in clinical trials. In a study of 80 therapy-naive patients, partial remission was seen in 4 patients. One received lanreotide alone, 1 interferon-α alone, and 2 received a combination of both agents. No complete remission was seen. There was a relatively short study period of 12 months, but the authors claim that both agents exhibited antiproliferative effects. This study included 26 patients with pancreatic endocrine tumors, but unfortunately no results were presented on this subset of patients.

Radiolabeled SST Analogues

Because imaging with radiolabeled somatostatin analogues has been effective for imaging, it has been thought that one might be able to deliver targeted therapeutic radiation to tumor cells using a similar methodology. To that end, several investigators have been trying to develop a high affinity somatostatin analogue linked to a high-energy β-emitting isotope for therapy. In 1996, a dodecanetetra-acetic acid-chelated somatostatin with high affinity for somatostatin receptor subtypes 2 and 5, labeled with ^{90}yttrium was developed. Radiolabeled somatostatin analogues are an exciting area of ongoing investigation. The high density of somatostatin receptors present on islet cell tumors is being investigated as a method to administer directed radiolabeled somatostatin analogues for cytotoxicity, a process referred to as peptide receptor radionuclide radiotherapy. Initial studies using high doses of [^{111}In-DTPA^{0}]octreotide demonstrated that this agent can be delivered safely with potential therapeutic efficacy. Significant responses, however, were uncommon.[285,286] Since then, other investigators have identified additional radiolabeled somatostatin analogues such as [DOTA^{0},Tyr^{3}]octreotate that have higher affinity for the somatostatin receptor.[287] The uptake of radioactivity for [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate was comparable to that for [^{111}In-DTPA^{0}]octreotide for kidney, spleen, and liver but was 3- to 4-fold higher for tumors.[288] In a recent clinical trial using [^{177}LuDOTA^{0},Tyr^{3}]octreotate in a series of 131 patients, Kwekkeboom and colleagues showed a complete remission in 3 (2%), partial remission in 32 (26%), tumor diameter decrease 25% to 50% (minor response) in 24 (19%), stable disease in 44 (35%), and progressive disease in 22 (18%).[289] Higher remission rates were positively correlated with high uptake on pretherapy SRS imaging and a limited number of liver metastases. Progressive disease was significantly more frequent in patients with extensive disease. The median time to progression in 103

patients who had either stable disease or tumor regression was more than 36 months. The majority of patients in this study had carcinoid tumors, with only 8 having metastatic gastrinoma. Patients with gastrinoma had a shorter time to progression than other patients. These results are difficult to interpret in light of the small number of patients with gastrinoma who were treated.[288]

Cytotoxic Agents

In 1992, Moertel and colleagues[290] published their classic study on the use of chemotherapy for metastatic islet cell tumors. In this multicenter trial, patients who had unresectable or metastatic islet cell carcinoma were randomly assigned to receive 1 of 3 chemotherapy regimens. These included streptozocin plus fluorouracil, streptozocin plus doxorubicin, or chlorozotocin alone.[290] This study included 105 patients who were not categorized by their specific islet cell neoplasm subtype. Response was determined by both changes in tumor size as documented by CT scan and/or by reduction of hormonal abnormalities. The streptozocin-doxorubicin combination group had the highest response rates, with 69% of patients showing documented tumor regression. Median survival rates were also highest for the streptozocin-doxorubicin group (2.2 years), compared with the streptozocin-fluorouracil (1.4 years) and streptozocin only groups (1.5 years). The degree to which this study can be extrapolated to nonfunctioning islet cell neoplasms is unclear, but there does appear to be benefit in using different chemotherapeutic regimens in the management of nonoperable disease. Other difficulties with this study result from the lack of a matched, nonchemotherapeutic control group.

A recent study reported on 15 patients with nonpulmonary neuroendocrine tumors including 6 of pancreatic origin, who received infusional 5-fluorouracil, folinic acid, and streptozocin.[291] One patient achieved a complete response, 7 demonstrated partial response, and 2 patients exhibit stable disease. The overall objective response rate, therefore, was 53%. The median time to progression for all patients was 4 months and 12 months for those who responded to treatment. Eight patients were alive at 27 month median follow-up interval. In preclinical experiments with the proteasome inhibitor bortezomib, antitumor activity was seen in a variety of solid tumors including the PC-12 neuroendocrine pheochromocytoma tumor cell line prompting a clinical study.[292] In a phase II study of 12 patients with metastatic carcinoid tumors and 4 with metastatic islet cell cancers treated with bortezomib, no patient achieved either a partial response or a complete remission.[293]

Two abstracts were presented at the 2005 American Society of Clinical

Oncology meeting dealing with chemotherapy regimens for neuroendocrine tumors. Kegel and colleagues studied 13 patients treated with paclitaxel, carboplatin, and etoposide.[294] This regimen was originally reported by Hainsworth and colleagues in 1997 for use in patients with carcinomas of unknown primary including poorly differentiated neuroendocrine carcinoma.[295] Kegel and colleagues found that in a cohort of 13 patients, 3 patients had a complete response, 2 had partial responses, and 5 had stable disease. The regimen was well tolerated and the median progression-free survival was more than 18 months. Another regimen presented at the same meeting was used in patients with low-grade neuroendocrine cancers who have failed other chemotherapy regimens or octreotide. Of 10 patients treated with tomozolomide and capecitabine, 6 were evaluable for response.[296] One had a durable complete response after 18 months, 2 had partial responses, and 3 had stable disease.

Chemotherapy is usually reserved for patients with disease progression or uncontrolled symptoms despite other therapy. Several chemotherapeutic agents including streptozocin, doxorubicin, 5-fluorouracil, chlorazotocin, dacarbazine, and interferon-α have been reported to have activity in islet cell tumors. Used as single drug therapy, overall response rates of up to 30% have been reported for these agents.[297-301]

The Eastern Cooperative Oncology Group (ECOG) compared combination chemotherapy using streptozocin and doxorubicin or streptozocin and 5-fluorouracil versus single agent therapy with the investigational agent chlorozotocin. The results of this study demonstrated a major response rate of 69% in patients treated with streptozocin and doxorubicin compared with a 45% response rate in patients treated with streptozocin plus 5-fluorouracil and a 30% response rate using chlorozotocin alone. The overall survival was significantly better in the streptozocin-and-doxorubicin-treated group, establishing this regimen as the standard of care for metastatic neuroendocrine tumors requiring chemotherapy.[302]

After adopting the regimen of streptozocin plus doxorubicin as their standard treatment, investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) reported their experience. They failed to confirm the findings of the ECOG trial. They found that, using standard CT response criteria, only 6% of patients achieved a major objective response when treated with the combination of streptozocin and doxorubicin.[303] These authors suggested that 1 possible explanation for the differences was the response criteria. At MSKCC, response was determined using CT findings. In older studies, assessment of hepatomegaly on physical examination, measurement of liver size on a liver-spleen scan, or a biologic response determined by a decrease in serum gastrin levels by

more than 50% were used to determine response. If the MSKCC group included reduction in liver size as part of their response criteria, the percentage of their patients with an objective response would have increased from 6% to 25%.[303]

Investigators at the M.D. Anderson Cancer Center performed a preliminary study using 3 agents: doxorubicin, streptozocin, and 5-fluorouracil. They found that 6 of 11 (54%) evaluable patients achieved a partial response, 1 had a minor response, and 2 had stable disease while 2 had progression of disease. The median response duration was 15 months.[304] This prompted a larger study using this 3-drug regimen. In the subsequent study, investigators enrolled 84 patients with locally advanced or metastatic neuroendocrine tumors, including 11 with gastrinomas. The response rate in this study was 39% with a median duration of 9.3 months. The 2-year progression-free survival rate was 41% and the 2-year overall survival rate was 74%. The extent of liver metastatic disease correlated with a worse progression-free survival.[305] Interestingly, none of the 11 patients with metastatic gastrinoma responded to chemotherapy, which contrasted with a 45% response rate in all other tumor types.[291] In a second study that included only patients with gastrinomas treated with streptozocin, doxorubicin, and 5-fluorouracil, the response rate was 40%.[306] Again, there were differences in the criteria used to determine response, which may in part explain the discrepancy. The results of these studies confirm the need for continued research into the biologic features of gastrinoma to better identify treatment agents.

Radiation Therapy

Some authors have published the benefits of using radiation for both the diagnosis and treatment of advanced islet cell cancer. Van Eijick and colleagues in the Netherlands used somatostatin receptor scintigraphy (SRS) to differentiate between primary pancreatic islet cell tumors and pancreatic adenocarcinomas as well as to identify previously unrecognized metastasis. The SRS used radionucleotide-labeled octreotide to visualize the islet cell tumor in 31 of 48 patients (65%) confirmed to have the disease. None of the tumors in 26 patients with confirmed adenocarcinoma were visualized with the SRS. The SRS appeared to detect nonfunctioning neoplasms as well as or better than functioning neoplasms. This group concluded that SRS can be a useful adjunct in the preoperative evaluation of islet cell neoplasms to determine the extent of disease. Despite the generally held belief that islet cell tumors are resistant to radiation therapy, there are case reports that document either partial or complete remission following treatment with this modality.

Tennvall and colleagues[13] in 1992 described a 63-year-old man with an unresectable, nonfunctioning islet cell tumor (due to encasement of the portal vein and hepatic artery at laparotomy) who received 40 Gy of external beam radiation over 30 days. Abdominal CT scan and angiography at 6 weeks following therapy revealed no demonstrable tumor. This patient underwent a second laparotomy 5 months following the radiotherapy. The pancreas was completely mobilized and determined to be free of masses. Biopsies taken from surrounding fibrotic lymph nodes were free of disease. The patient was alive and free of disease by abdominal CT scan at 17 months following completion of radiotherapy.

Torrisi and colleagues followed 9 patients that received external beam radiation, intraoperative radiation, and/or ^{125}I implants for advanced disease. All of these patients experienced complete resolution of pain or other symptoms following therapy. Only 1 patient had a relatively long period of remission and remained asymptomatic at 3 years, 9 months following therapy. Radiotherapy remains an option for patients with advanced disease who are not amenable to surgery for nonfunctioning islet cell tumors. The lack of prospective randomized evidence, combined with its dose-limiting small bowel toxicity, limit its use as first line therapy at this time.

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