

Use of Endoscopy in the Diagnosis of a Patient With an ACTH-producing Pancreatic Tumor

Corlan O. Adebajo, MD¹

Charles Dye, MD²

John Liang, MD³

Matthew T. Moyer, MD²

¹Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; ²Division of Gastroenterology and Hepatology, ³Department of Pathology and Laboratory Medicine, The Pennsylvania State College of Medicine, Hershey, Pennsylvania

Case Report

A 66-year-old man was suspected of having acute Cushing syndrome based upon the following symptoms: hyperglycemia; hypokalemic alkalosis; an elevated serum total cortisol level of 41.0 µg/dL (normal, 2.9–19.4 µg/dL), which did not respond to corticotrophin-releasing hormone stimulation; and adrenocorticotrophic hormone (ACTH) levels of 121–146 pg/mL (normal, 20–80 pg/mL), which were not suppressed by either low- or high-dose dexamethasone. Magnetic resonance imaging of the patient's pituitary was negative; however, computed tomography (CT) imaging of the chest, abdomen, and pelvis suggested a vague 1.7-cm × 2.4-cm mass-like abnormality in the uncinate process and bilateral adrenal thickening (Figure 1).

The patient was referred for endoscopic ultrasound (EUS) and fine-needle aspiration (FNA) evaluation of the pancreas. A linear EUS examination clearly revealed a 2.4-cm × 2.4-cm hypoechoic heterogenic uncinate mass with regular borders and without cystic features (Figure 2), which was consistent with a T2N0MX neuroendocrine tumor based upon EUS criteria. Tissue evaluation was performed using 2 passes each of 25- and 22-gauge FNA needles as well as a core biopsy. Pathologic evaluation of both the fine-needle aspirates and the core biopsies demonstrated uniform neoplastic cells, small to medium in size, with scant cytoplasm, oval nuclei with coarse chromatin, and a solid nesting

pattern (Figure 3). Immunoperoxidase stains showed strong cytoplasmic staining within the tumor cells for antibodies directed against ACTH (Figure 4).

The patient underwent a successful pancreaticoduodenectomy. Postoperatively, his ACTH level decreased from 121 pg/mL to 21 pg/mL, confirming the diagnosis of an ectopic ACTH-secreting tumor (Cushing syndrome).

Discussion

Approximately two thirds of patients with symptoms consistent with Cushing syndrome actually have Cushing disease, an ACTH-secreting pituitary tumor.¹ Cushing

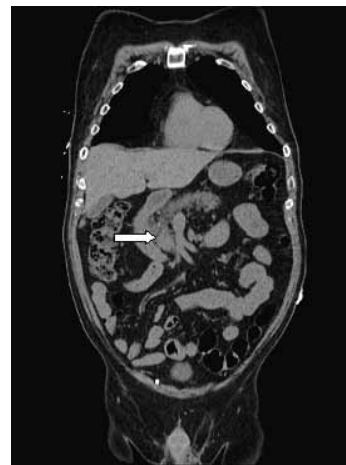


Figure 1. Coronal computed tomography image of the chest, abdomen, and pelvis. The arrow reveals a 1.7-cm × 2.4-cm mass at the uncinate process.

Address correspondence to:

Dr. Corlan O. Adebajo, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; E-mail: adebajo.corlan@mayo.edu



Figure 2. Linear endoscopic ultrasound of a 2.4-cm × 2.4-cm hypoechoic heterogenic uncinate mass.

syndrome secondary to ectopic ACTH production is a relatively uncommon clinical condition that accounts for up to 16% of patients with ACTH-dependent hypercortisolism.^{1,2} These patients have elevated cortisol and ACTH levels and frequently have CT scans that show bilateral adrenal enlargement.³ The most common ectopic ACTH-secreting tumors are bronchial and thymic carcinoids, with pancreatic islet cell tumors being responsible for less than 1% of all causes of Cushing syndrome.¹

Although the chronic syndrome is often clinically indistinguishable from pituitary-dependent hypercortisolism presenting with plethora, truncal obesity, buffalo hump, and red striae, the typical Cushing habitus is absent in many acute cases.⁴ Acute Cushing syndrome, which is how our patient presented, is more often associated with the rapid onset of hypertension, weakness, edema, hypokalemia, glucose intolerance, anorexia, and weight loss.⁴

Dynamic testing based upon differential sensitivity to glucocorticoid feedback or ACTH stimulation in response to corticotropin-releasing hormone or cortisol reduction is a reliable way to discern between an ectopic versus a pituitary source of excess ACTH.⁵ High-dose dexamethasone suppresses morning serum cortisol levels in approximately 80% of pituitary ACTH-producing adenomas, though it fails to suppress ACTH in approximately 90% of ectopic cases. However, bronchial and other carcinoids are well-documented exceptions to these general guidelines, as these ectopic sources of ACTH may exhibit feedback regulation indistinguishable from pituitary adenomas.⁵

Although approximately 90% of patients with ectopic ACTH-producing tumors can be cured by surgical resection, pancreatic tumors are virulent neoplasms associated with a rapidly progressive clinical course.¹ In a retrospective analysis of patients with pancreatic islet cell tumors associated with Cushing syndrome, 60% of patients died

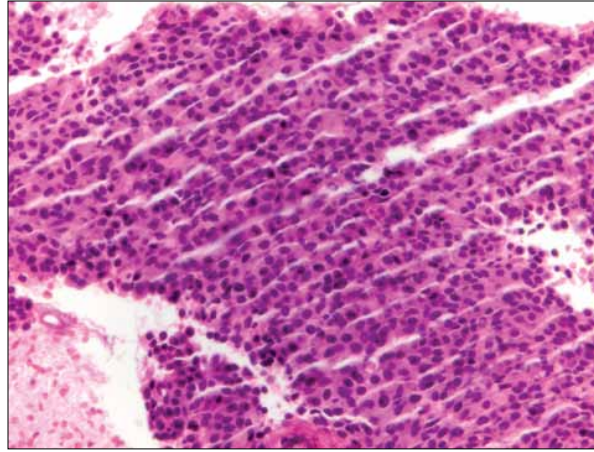


Figure 3. Uniform neoplastic cells, small to medium in size, with scant cytoplasm, oval nuclei with coarse chromatin, and a solid nesting pattern (hematoxylin & eosin stain, 40×).

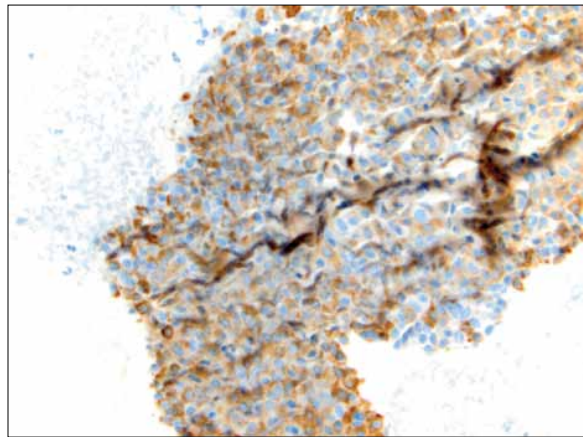


Figure 4. Strong cytoplasmic staining within the tumor cells for antibodies directed against adrenocorticotropic hormone (immunohistochemical stain, 40×).

within 2 years, and the 5-year survival rate was reported to be 16%.⁶ Patients with ectopic ACTH secretion may be at risk of death from metastasis and infections caused by the immunosuppressive effects of excess adrenocortical steroid.⁶ Therefore, functioning pancreatic tumors should be operated early on in the course of the disease to provide a cure.⁷ The optimal treatment for patients with ectopic ACTH production is localization and surgical excision of the source of the ACTH secretion.¹ Successful surgical excision depends upon the ability to identify the site of the tumor and the resectability and metastatic capacity of the neoplasm before operation.¹

References

1. Amikura K, Alexander HR, Norton JA, et al. Role of surgery in management of adrenocorticotrophic hormone-producing islet cell tumors of the pancreas. *Surgery*. 1995;118:1125-1130.
2. Lee T, Karl M, Solorzano CC. Adrenocorticotrophic hormone-secreting pancreatic islet cell carcinoma. *J Am Coll Surg*. 2004;199:336-337.
3. Uecker JM, Janzow MT. A case of Cushing syndrome secondary to ectopic adrenocorticotrophic hormone producing carcinoid of the duodenum. *Am Surg*. 2005;71:445-446.
4. Miehle K, Tannapfel A, Lamesch P, et al. Pancreatic neuroendocrine tumor with ectopic adrenocorticotrophic production upon second recurrence. *J Clin Endocrinol Metab*. 2004;89:3731-3736.
5. Jameson JL, Johnson BE. Paraneoplastic syndromes: endocrinologic/hematologic. In: Fauci AS, Braunwald E, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York, NY: McGraw-Hill Professional; 2008:617-623.
6. Clark ES, Carney JA. Pancreatic islet cell tumor associated with Cushing syndrome. *Am J Surg Pathol*. 1984;8:917-924.
7. Plöckinger U, Wiedenmann B. Neuroendocrine tumors of the gastro-entero-pancreatic system: the role of early diagnosis, genetic testing and preventive surgery. *Dig Dis*. 2002;20:49-60.

Review

Diagnosis of Pancreatic Neuroendocrine Tumors and the Role of Endoscopic Ultrasound

Linda S. Lee, MD

Center for Pancreatic Disease, Therapeutic Endoscopy, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Pancreatic neuroendocrine tumors (PETs) such as the one described in the interesting case report by Adebajo and associates¹ are exceedingly rare but generate much clinical interest due to their protean and often dramatic manifestations. They comprise 1–2% of all pancreatic neoplasms. The annual incidence of clinically symptomatic PETs is less than 1 in 100,000, although the prevalence of asymptomatic PETs in autopsy studies is higher, ranging from 0.8% to 10%.^{2,3} Nonfunctioning PETs are most common, accounting for 70–90% of all PETs,³ followed by insulinomas and gastrinomas, whereas vasoactive intestinal peptide-producing tumors, glucagonomas, somatostatinomas, and others occur very rarely, in decreasing order of incidence. Among the other hormones secreted by PETs extremely rarely are growth hormone–releasing factor, parathyroid hormone–related protein, and adre-

nocorticotrophic hormone (ACTH). Although PETs do occur sporadically, they have a much higher incidence (30–75%) in patients with the hereditary syndrome multiple endocrine neoplasia-type 1 (MEN-1). Other inherited syndromes less commonly associated with PETs include von Hippel-Lindau disease, von Recklinghausen disease, and tuberous sclerosis.

Clinically, PETs are classified as nonfunctional or functional, depending upon the absence or presence of clinical symptoms related to hormone release. Therefore, nonfunctional PETs may not secrete hormones, or the secreted hormones may not produce symptoms. Accordingly, nonfunctional PETs are larger and more often malignant at presentation than functioning PETs.⁴ Malignancy is defined by the invasion of adjacent organs, spread to lymph nodes, or presence of distant metastases, and is not strictly based upon histology. The World Health Organization classifies PETs into the following categories: well-differentiated endocrine tumors with benign or unknown behavior; well-differentiated endocrine carcinomas with low-grade malignant potential; or poorly differentiated endocrine carcinomas with high-grade malignant potential.⁵ A tumor lymph node metastasis (TNM) classification analogous to the TNM system for other solid tumors has also been developed.⁶ Both appear to accurately predict long-term survival for PETs.⁷ Recent data have also suggested the ability to prognosticate from endoscopic ultrasound–fine needle aspirate (EUS-FNA) specimens of PETs. Malignant PETs contained significantly greater DNA microsatellite losses than benign lesions, and more microsatellite loss was associated with higher 2-year recurrence and lower 5-year survival.⁸

Other factors influencing prognosis include the type of PET, primary tumor size and location, extent or rate of growth of liver metastases, presence of bone metastases, histologic features, high proliferative indices, flow cytometric features, and development of ectopic Cushing

Address correspondence to:

Dr. Linda S. Lee, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115; Tel: 617-732-7429; E-mail: lslee@partners.org

syndrome. Although insulinomas have low malignant potential (5–15%), the other PETs have a much higher malignant potential, ranging from 50% to 90%, with a greater-than-90% malignancy rate in ACTH-producing PETs. ACTH-producing PETs metastasize early (occasionally even before clinical manifestation of Cushing syndrome) and frequently to the liver, leading to a poor 5-year survival rate of 16%.⁹ Therefore, it is certainly unusual that the patient in this case study did not present with metastatic disease.

Diagnosis of functional PETs is guided by clinical symptomatology. For suspected insulinomas, serum glucose, insulin, proinsulin, and C peptide levels should be checked, with a prolonged 72-hour fast as the gold standard for diagnosis. In potential gastrinomas, fasting serum gastrin, basal acid output, and secretin tests may be used for diagnosis. Serum vasoactive intestinal peptide, glucagon, and somatostatin levels are diagnostic for their respective PETs. Diagnosis of ectopic ACTH-PET, as outlined in this case, involves documentation of hypercortisolism, typically with late-night serum cortisol, followed by demonstration of ACTH dependence with elevated ACTH, and finally unresponsiveness to glucocorticoid feedback using the high-dose dexamethasone suppression test and corticotropin-releasing hormone test, which implies an ectopic, nonpituitary source of ACTH. Chromogranin A is widely used to diagnose and follow especially nonfunctional PETs, with a sensitivity of 60–100% in metastatic disease but only 50% for local disease.¹⁰

With a biochemical diagnosis, radiologic studies are critical to identify the location of the tumor as well as metastases in order to guide appropriate management. This approach can be challenging, particularly with functional tumors, which are often small. Traditional radiologic imaging with computed tomography (CT) scan is 64–82% sensitive for detecting the primary tumor, whereas magnetic resonance imaging (MRI) has an equivalent or superior sensitivity of 74–100%.¹¹ Classically, PETs demonstrate hypervascular enhancement during the arterial phase of CT due to their vascular nature. Because PETs often contain somatostatin receptors, functional imaging with somatostatin receptor scintigraphy (SRS) identifies 50–70% of primary tumors, with the exception of insulinomas that express somatostatin receptors in only approximately half of cases.¹⁰ Other limitations of SRS include reduced accuracy in localizing the tumor within the pancreas, differentiating between an intrapancreatic lesion and a peripancreatic lymph node, and detecting small PETs less than 1 cm in size. Positron-emission tomographic scanning with standard substrates such as ¹⁸F-deoxyglucose is ineffective due to the low metabolic activity of most PETs; however, use with ¹¹C-5-hydroxy-

tryptophan (¹¹C-5-HTP) or ⁶⁸Ga-labeled somatostatin analogues appears very promising.¹² With the advent of functional imaging and ever-improving CT and MRI, invasive angiographic techniques involving arterial stimulation with secretagogues and subsequent selective hepatic venous sampling are infrequently utilized.

Given the limitations of the current radiologic studies, EUS has become an integral part of the diagnosis of PETs because of its high sensitivity for detecting, localizing, and diagnosing pancreatic PETs. In fact, when a lesion is not visualized on CT scan in patients with PETs, sensitivity of EUS-FNA for diagnosing PETs is 70%.¹³ In an older series of 82 patients with suspected PETs due to clinical, biochemical, or radiologic evidence, the sensitivity, specificity, and accuracy of EUS imaging for localizing PETs was 93%, 95%, and 93%, respectively.¹⁴ Other studies have reported sensitivity rates of EUS ranging from 83% to 94% for detecting PETs.^{15,16}

Most commonly, PETs appear hypoechoic, round, homogeneous, and well defined on EUS, though they may be isoechoic and, on rare occasions, hyperechoic with irregular margins. Malignant PETs are larger, with irregular margins, compared to benign PETs. Cystic lesions are the least common presentation, accounting for 8–17% of PETs, and may be unilocular, septated, microcystic, or mixed solid-cystic.^{17,18} Compared to solid PETs, cystic PETs are twice as large, more often symptomatic, 3.5 times more likely to be associated with MEN-1, and more likely nonfunctional.¹⁸ Approximately 81% of cystic PETs are nonfunctional, and diagnosis with radiologic or EUS imaging alone is unlikely due to the lack of distinguishing characteristics of these cystic lesions. Therefore, cytologic and immunohistochemical evaluation of EUS-FNA specimens is essential and appears to have similar sensitivity as EUS-FNA of solid PETs.¹³

The addition of FNA to EUS using a 22- or 25-gauge needle enables tissue diagnosis, which allows differentiation from pancreatic adenocarcinoma and is more relevant for diagnosis of nonfunctioning or cystic PETs. One could argue that FNA was not essential in the current case, given a biochemical diagnosis of ectopic ACTH syndrome with a mass seen on EUS. Two recent large studies of EUS-FNA in PETs reported overall 87–90% sensitivity, with one study finding diminished sensitivity (66%) for tumors that were smaller than 15 mm or benign, though the other publication failed to replicate these results.^{13,19} Although cytomorphology alone was adequate for diagnosis in one of these studies, the use of immunohistochemistry on cytology specimens, as in this case report, may aid in cytologic diagnosis of PETs.

To improve FNA yield, ideally onsite cytopathology examination should be performed. This examination significantly reduces the rate of unsatisfactory cytology

specimens from 20% to 9%.²⁰ If a cytopathologist is unavailable, 5–7 passes should be performed for pancreatic masses (as in this case), 2–3 for liver metastases, and 2–5 for lymph nodes.^{21,22} Use of a 22- versus a 25-gauge needle does not affect diagnostic yield, though comparative experience specifically with PETs is limited.²³ The trucut needle biopsy uses a 19-gauge needle to obtain core biopsies. Despite interest in this technique, studies have not consistently demonstrated superior diagnostic yield, and technical failures occur, particularly with the duodenal approach.²⁴ Therefore, lesions in the pancreatic head and uncinata process are difficult to access, and, again, there are inadequate data with PETs. EUS-guided brush of pancreatic cysts appears to have similar or possibly superior diagnostic yield to FNA; however, it may carry an increased bleeding risk.²⁵

Despite EUS and improved radiologic imaging, small PETs may be difficult to localize in the operating room. Intraoperative palpation combined with intraoperative ultrasound is over 95% sensitive; however, they prolong operative time, have rarely been associated with splenic vessel rupture from manipulation of the pancreas, and are not practical with laparoscopic resections.²⁶ Tattooing the lesion during EUS appears to be safe, according to small case series. The agents injected into the pancreas have included presterilized, diluted, and filtered India ink, indocyanine green, methylene blue, and GI Spot.^{27,28} EUS-fine needle injection with GI Spot lasted up to 83 days after injection, and operative time was significantly reduced, with no repeat surgery necessary in tattooed patients.²⁸

In conclusion, PETs are unusual entities offering an extraordinary glimpse into the workings of various hormones, including, on rare occasions, ACTH. Diagnosis of functional PETs usually relies upon biochemical and imaging studies, particularly EUS, given the smaller size of functional tumors. Nonfunctional PETs are more readily detected with radiology, though they will typically require EUS-FNA for definitive diagnosis. It is clear that endoscopy with EUS and EUS-FNA has become a cornerstone in the diagnosis of these fascinomas.

References

- Adebajo CO, Dye C, Liang J, Moyer MT. Use of endoscopy in the diagnosis of a patient with an ACTH-producing pancreatic tumor. *Gastroenterol Hepatol (N Y)*. 2010;6:518-520.
- Kimura W, Kuroda A, Morioka Y. Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. *Dig Dis Sci*. 1991;36:933-942.
- Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol*. 2008;19:1727-1733.
- Figueiredo FA, Giovannini M, Monges G, et al. Pancreatic endocrine tumors: a large single-center experience. *Pancreas*. 2009;38:936-940.
- Klöppel G, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann NY Acad Sci*. 2004;1014:13-27.
- Rindi G, Klöppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch*. 2006;449:395-401.
- Fischer L, Kleeff J, Esposito I, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. *Br J Surg*. 2008;95:627-635.
- Fasanella KE, McGrath KM, Sanders M, Brody D, Domsic R, Khalid A. Pancreatic endocrine tumor EUS-guided FNA DNA microsatellite loss and mortality. *Gastrointest Endosc*. 2009;69:1074-1080.
- Kondo T, Matsuyama R, Ashihara H, et al. A case of ectopic adrenocorticotrophic hormone-producing pancreatic neuroendocrine tumor with multiple liver metastases. *Endocr J*. 2010;57:229-236.
- Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology*. 2008;135:1469-1492.
- Tamm EP, Kim EE, Ng CS. Imaging of neuroendocrine tumors. *Hematol Oncol Clin North Am*. 2007;21:409-432.
- Sundin A, Garske U, Orlefors H. Nuclear imaging of neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab*. 2007;21:69-85.
- Pais SA, Al-Haddad M, Mohamadnejad M, et al. EUS for pancreatic neuroendocrine tumors: a single-center, 11-year experience. *Gastrointest Endosc*. 2010;71:1185-1193.
- Anderson MA, Carpenter S, Thompson NW, Nostrant TT, Elta GH, Scheiman JM. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. *Am J Gastroenterol*. 2000;95:2271-2277.
- Gouya H, Vignaux O, Augui J, et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. *AJR Am J Roentgenol*. 2003;181:987-992.
- Ardengh JC, Rosenbaum P, Ganc AJ, et al. Role of EUS in the preoperative localization of insulinomas compared with spiral CT. *Gastrointest Endosc*. 2000;51:552-555.
- Kongkam P, Al-Haddad M, Attasaranya S, et al. EUS and clinical characteristics of cystic pancreatic neuroendocrine tumors. *Endoscopy*. 2008;40:602-605.
- Bordeianou L, Vagefi PA, Sahani D, et al. Cystic pancreatic endocrine neoplasms: a distinct tumor type? *J Am Coll Surg*. 2008;206:1154-1158.
- Figueiredo FA, Giovannini M, Monges G, et al. EUS-FNA predicts 5-year survival in pancreatic endocrine tumors. *Gastrointest Endosc*. 2009;70:907-914.
- Klapman JB, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol*. 2003;98:1289-1294.
- Erickson RA, Sayage-Rabie L, Beissner RS. Factors predicting the number of EUS-guided fine-needle passes for diagnosis of pancreatic malignancies. *Gastrointest Endosc*. 2000;51:184-190.
- LeBlanc JK, Ciaccia D, Al-Assi MT, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. *Gastrointest Endosc*. 2004;59:475-481.
- Siddiqui UD, Rossi F, Rosenthal LS, Padda MS, Murali-Dharan V, Aslanian HR. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. *Gastrointest Endosc*. 2009;70:1093-1097.
- Varadarajulu S, Fraig M, Schmulewitz N, et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. *Endoscopy*. 2004;36:397-401.
- Al-Haddad M, Gill KR, Raimondo M, et al. Safety and efficacy of cytology brushings versus standard fine-needle aspiration in evaluating cystic pancreatic lesions: a controlled study. *Endoscopy*. 2010;42:127-132.
- Wong M, Isa SH, Zahirah M, Azmi KN. Intraoperative ultrasound with palpation is still superior to intra-arterial calcium stimulation test in localising insulinoma. *World J Surg*. 2007;31:586-592.
- Gress FG, Barawi M, Kim D, Grendell JH. Preoperative localization of a neuroendocrine tumor of the pancreas with EUS-guided fine needle tattooing. *Gastrointest Endosc*. 2002;55:594-597.
- Lennon AM, Newman N, Giday SA, et al. Endoscopic ultrasound-guided tattoo of pancreatic lesions decreases operative time in patients undergoing laparoscopic distal pancreatectomy. *Gastrointest Endosc*. 2010;71:AB136.